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(54) Title: PROCESS FOR PREPARATION OF TAXANE DERIVATIVES AND β-LACTAM INTERMEDIATES THEREFOR

(57) Abstract

Taxol (I) is a complex diterpene which is currently considered the most exciting lead in cancer chemotherapy. Taxol possesses high cytotoxicity and strong antitumor activity against different cancers which have not been effectively treated by existing antitumor drugs. However, taxol has a problem with solubility in aqueous media, which may impose some serious limitation in its use. TAXOTERE (III) seems to have antitumor activity superior to taxol with better bioavailability. Taxotère has a modified taxol structure with a modified C-13 side chain. This fact strongly indicates that modification on the C-13 side chain would provide a new series of taxol and TAXOTERE analogues which may have higher potency, better bioavailability and less unwanted toxicity. The present invention provides efficient and practical methods for the syntheses of TAXOTERE and its analogues through β-lactam intermediates and their coupling with baccatin III.

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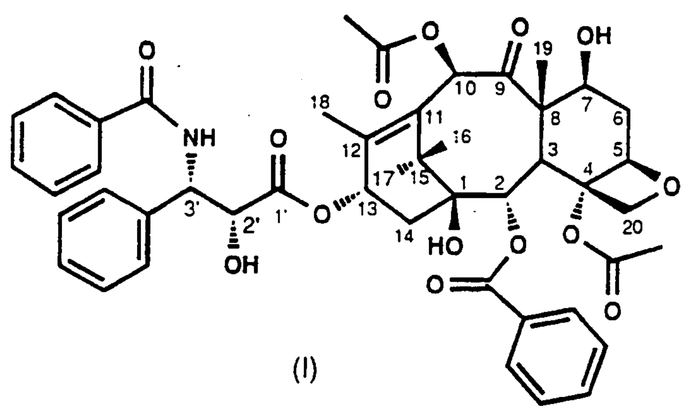
PROCESS FOR PREPARATION OF TAXANE DERIVATIVES AND ß-LACTAM INTERMEDIATES THEREFOR

FIELD OF THE INVENTION

The present invention relates to a process for the preparation of taxoid(s) including TAXOTÈRE and its analogs and the ß-lactam intermediates useful in this process.

BACKGROUND OF THE INVENTION

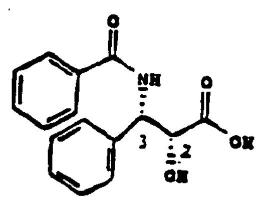
Taxol (I) is a complex diterpene which is currently considered the most exciting lead in cancer chemotherapy. Taxol possesses high cytotoxicity and strong antitumor activity against different cancers which have not been effectively treated by existing antitumor drugs. For example, taxol is currently in phase III clinical trials for advanced ovarian cancer, phase II for breast cancer, and phase I for lung cancers, colon cancer and acute leukemia.



(I)

Although taxol is an extremely important "lead" in cancer chemotherapy, taxol has a problem with solubility in aqueous media, which may impose some serious limitation in its use. It is common for improved drugs to be derived from naturally occurring lead compounds. In fact, French researchers, Potier, Guéritte-Voegelein,

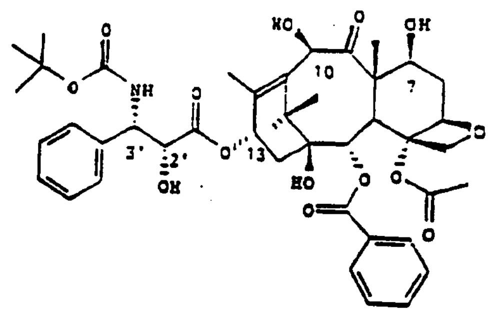
Guénard et al. have discovered that a modification of the C-13 side chain of taxol brought about a new anticancer agent which seems to have antitumor activity superior to taxol with better bioavailability. This synthetic compound was named "TAXOTÈRE (II)", which has t-butoxycarbonyl instead of benzoyl on the amino group of (2R,3S)-phenylisoserine moiety at the C-13 position and a hydroxyl group instead of an acetoxy group at C-10. [Colin, M. et al. Eur. Pat. Appl. EP253,738 (1988)]. Taxotère is currently in phase II clinical trial in both United States and Europe. TAXOTÈRE has been synthesized by a semisynthetic process, including a coupling of N-tert-butoxycarbonyl-(2R,3S)-3-phenylisoserine with 10-deacetylbaccatin III with proper protecting groups. (Denis, J.-N. recently reported (Commercon, A. et al., Tetrahedron Letters, 1992, 33 5185)).



(II)

It is known that the C-13 side chain of taxol, i.e., N-benzoyl-(2R, 3S)-3-phenylisoserine (III) moiety, is crucial for the strong antitumor activity of taxol. (Senilh et al., C.R. Séancas Acad. Sci. Ser. 2 1984, 299, 1039; Guéritte-Voegelein et al., Tetrahedron, 1986, 42, 4451, and Mangatal et al., Tetrahedron, 1989, 45, 4177; Guéritte-Voegelein et al. J. Med. Chem. 1991, 34, 992; and Swindell et al., J. Med. Chem. 1992, 35, 145; Mathew, A.E. et al., J. Med. Chem. 1992, 35, 145). Moreover, some modification of the C-13 side chain can provide a new series of taxol analogs which may have higher potency, better bioavailability and less unwanted toxicity, as

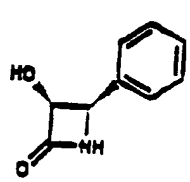
exemplified by the discovery of TAXOTÈRE (II).



(III)

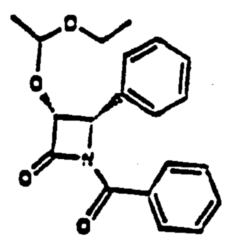
Accordingly, the development of an efficient method which can be applied to various analogs of taxol and TAXOTÈRE and analogs thereof, i.e., a method having flexibility and wide applicability, is extremely important and of current demand. It has been shown that such a new and efficient method with flexibility can be developed by using enantiomerically pure β-lactams as key-intermediates [Ojima, I. et al., J. Org. Chem., 1991, 56, 1681; Ojima et al., Tetrahedron, 1992, 48, 6985; Holton, R.A., Eur. Patent Appl. EP 400,971 (1990)].

Lithium chiral ester enolate-imine cyclocondensation strategy has been applied to the asymmetric synthesis of the side chain of taxol via a (3*R*,4*S*)-3-hydroxy-4-phenylazotidin-2-one (IV) as the key-intermediate. (Ojima, I. et al., J. Org. Chem., 1991, 56, 1681; Ojima et al., Tetrahedron, 1992, 48, 6985)



(IV)

Based on this protocol, the side chain can be obtained in 3 steps in high yield with virtually 100% e.e. (Ojima, I. et al. J. Org. Chem. 1991 56, 1681). Recently, it was found that 1-benzoyl-(3*R*,4*S*)-3-(1-ethoxyethoxy)-4-phenylazetidin-2-one (V), readily derived from the hydroxy-ß-lactam (IV), served as the key-intermediate for the synthesis of taxol [Holton, R.A. Eur. Pat. Appl. EP 400,971 (1990)]. Therefore, this ß-lactam intermediate serves as the key-intermediate for both coupling methods.



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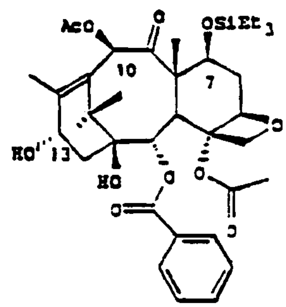
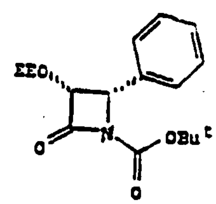


7-TES-baccatin III (VI)

In the published European application to Holton (hereinafter Holton), the ß-lactam intermediate (V) was

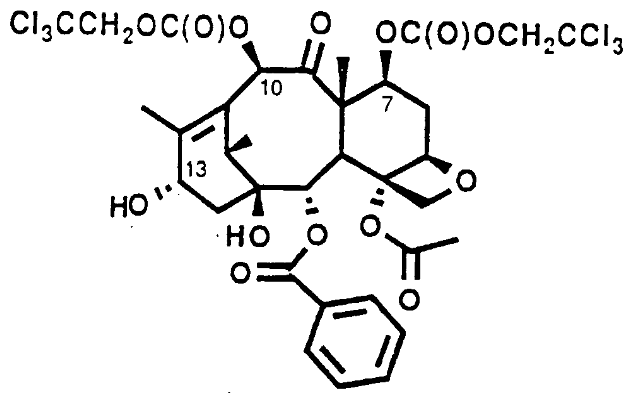
obtained through tedious optical resolution of the racemic cis-3-hydroxy-β-lactam. According to Holton's procedure, the coupling of the β-lactam (V) with 7-triethylsilylbaccatin III (VI) (7-TES-baccatin III) proceeds at 25°C in the presence of dimethylaminopyridine (DMAP) and pyridine for 12 hours to give protected taxol in 92% yield, which was deprotected with 0.5% hydrochloric acid in ethanol at 0°C to afford taxol in ca. 90% yield.

However, the Holton procedure did not work at all when 1-tert-butoxycarbonyl-(3*R*,4*S*)-3-(1-ethoxylethoxy)-4-phenylazetidin-2-one (VII) was used for the attempted synthesis of TAXOTÈRE (II) by the present inventors.



(VII)

It is believed that this may be due to the lack of reactivity of the 1-tert-butoxycarbonyl-β-lactam (VII) toward the C-13 hydroxyl group of a protected baccatin III (VI or VIII) under the conditions used by Holton. The lack of reactivity may be ascribed to the substantially weaker electron-withdrawing ability of tert-butoxycarbonyl group than that of benzoyl group.



7.10-di-Troc-10-deacetylbaccatin III (VIII)

Therefore, it was an objective of the present invention to develop a new method which can achieve the coupling of the 1-tert-butoxycarbonyl-ß-lactam (VII) with the protected baccatin III (VIII) for the synthesis of TAXOTÈRE (II).

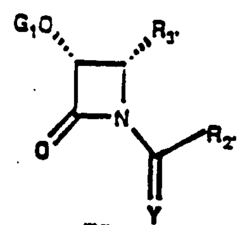
All of the references cited above and any reference which may be mentioned herein below are expressly incorporated into the present disclosure.

It is an object of the present invention to provide new ß-lactams useful in the syntheses of TAXOTÈRE (II) and analogs thereof.

It is further object of the present invention to provide a new coupling method for the syntheses of TAXOTÈRE (II) and analogs thereof.

SUMMARY OF THE INVENTION

A ß-lactam of the formula (IX)



(IX)

in which

$R_{2'}$ represents an RO-, RS- or RR'N- in which R represents an unsubstituted or substituted straight chain or branched alkyl, alkenyl or alkynyl, cycloalkyl, heterocycloalkyl, cycloalkenyl, heterocycloalkenyl, carbocyclic aryl or heteroaryl, wherein substituents bearing one or more active hydrogens such as hydroxyl, amino, marcapto and carboxyl groups are protected; R' is a hydrogen or R as defined above; R and R' can be connected to form a cyclic structure; Examples of $R_{2'}$ include methoxy, ethoxy, isopropoxy, tert-butoxy, neopentyloxy, cyclohexyloxy, allyloxy, propargyloxy, adamantyloxy, phenyoxy, 4-methoxyphenoxy, 2-fluorophenoxy, 4-methoxycarbonylphenoxy, methylthio, ethylthio, isopropylthio, tert-butylthio, neopentylthio, cyclohexylthio, phenylthio, 3,4-dimethoxyphenylthio, methylamino, ethylamino, isopropylamino, tert-butylamino, neopentylamino, cyclohexylamino, dimethylamino, pyrrolidino, piperidino and morpholino group.

$R_{3'}$ represents an unsubstituted or substituted straight chain or branched alkyl, alkenyl or alkynyl

radical, an unsubstituted or substituted cycloalkyl, or cycloalkenyl radical, an unsubstituted or substituted aryl radical wherein substituents bearing one or more active hydrogens such as hydroxy, amino, mercapto and carboxyl groups are protected; Examples of R_3, include phenyl, 4-methoxyphenyl, 3,4-dimethoxylphenyl, 4-fluorophenyl, 4-trifluoromethylphenyl, 4-chlorophenyl, 4-bromophenyl, naphthyl, cyclohexyl, cyclohexylmethyl, 2-phenylethenyl, 2-phenylethyl, benzyl, neopentyl, tert-butyl, isobutyl, isopropyl, allyl and proparagyl;

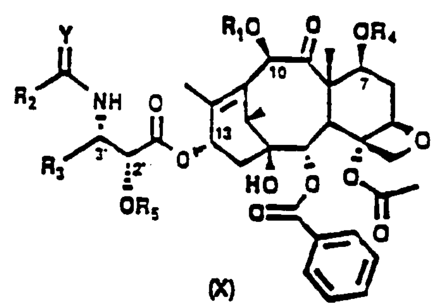
G_1 represents a hydrogen or hydroxyl protecting group such as methoxymethyl (MOM), methoxylethyl (MEM), 1-ethoxyethyl (EE) benzyloxymethyl, (ß-trimethylsilylethoxyl)methyl, tetrahydropyranyl, 2,2,2-trichloroethoxycarbonyl (Troc), tert-butoxycarbonyl (t-BOC), 9-fluorenylmethoxycarbonyl (Fmoc), 2,2,2-tricholoroethoxymethyl, trimethylsilyl, triethylsilyl, dimethylethylsilyl, dimethyl(t-butyl)silyl, diethylmethylsilyl, dimethylphenylsilyl and diphenylmethylsilyl;

Y is oxygen or sulfur.

The present inventor investigated the ß-lactam coupling reaction with protected Baccatin III in detail and found that the coupling could be achieved by increasing the nucleophilicity of the 13-hydroxyl group of a protected baccatin III (VI or VIII) through transformation of the hydroxyl group to the corresponding metal alkoxide. Such a C-13 metal alkoxide of a baccatin III was readily generated by reacting the baccatin III (VI or VIII) with an alkali or alkaline earth metal base. This finding is the basis of the present invention. The method of the present invention not only enables the coupling of the ß-lactam (VII) and its derivatives and analogs with a protected baccatin III, but also requires only a stoichiometric amount of the ß-lactams. The latter makes a sharp contrast with the Holton procedure for taxol

synthesis which needs 5-6 equivalents of the more reactive ß-lactam (V). Moreover, the coupling reactions of the present invention proceeds very smoothly and complete typically within 30 minutes at -30°C - 0°C.

The present invention also relates to a process for the preparation of taxane derivatives of the formula (X)



(X)

in which

R_1 represents a hydrogen atom or an acyl or an alkyl or an alkenyl or an alkynyl or carbocyclic aryl or a heteroaryl radical or a hydroxyl protecting group (G_1 defined above);

R_2 represents an RO-, RS- or RR'N- in which R represents an unsubstituted or substituted straight chain or branched alkyl, alkenyl or alkynyl, cycloalkyl, heterocycloalkyl, cycloalkenyl, heterocycloalkenyl, carbocyclic aryl or heteroaryl; R' is a hydrogen or R as defined above; R and R' can be connected to form a cyclic structure;

Y is oxygen or sulfur;

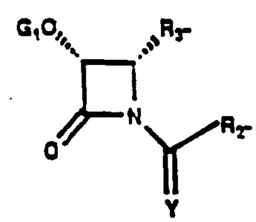
R_3 represents an unsubstituted or substituted straight chain or branched alkyl, alkenyl radical, an

unsubstituted or substituted cycloalkyl, cycloalkenyl radical or an unsubstituted or substituted carbocyclic aryl radical;

R_4 represents a hydrogen or an acyl radical or an unsubstituted or substituted straight chain or branched alkyl, alkenyl or alkynyl radical, an unsubstituted or substituted cycloalkyl, heterocycloalkyl, cycloalkenyl or heterocycloalkenyl radical, an unsubstituted or substituted carbocyclic aryl or heteroaryl radical, or a hydroxyl group protecting group (G_1 defined above);

R_5 represents a hydrogen or an acyl radical or an unsubstituted or substituted straight chain or branched alkyl, alkenyl or alkynyl radical, an unsubstituted or substituted cycloalkyl, heterocycloalkyl, cycloalkenyl or heterocycloalkenyl radical, an unsubstituted or substituted carbocyclic aryl or heteroaryl radical, or a hydroxyl protecting group (G_1 defined above);

which comprises condensing a ß-lactam of the formula



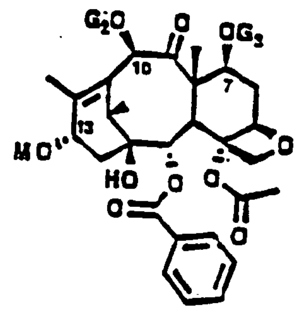
in which

Y and G_1 are defined above;

$R_{2'}$ represents a radical R_2 as defined above or a protected R_2 whenever R_2 includes one or more active hydrogens such as hydroxyl, amino, mercapto and carboxyl groups;

$R_{3'}$ represents a radical as R_3 defined above or a protected R_3 whenever R_3 includes one or more active

hydrogens such as hydroxyl, amino, mercapto and carboxyl groups; with a baccatin III derivative of the formula:



in which

M is an alkali metal or alkaline earth metal atom (ion);

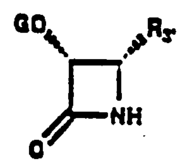
G_2 represents a hydroxyl protecting group (G_1 defined above) or an acyl radical or an unsubstituted or substituted straight chain or branched alkyl, alkenyl or alkynyl radical, an unsubstituted or substituted cycloalkyl, heteroycloalkyl, cycloalkenyl or heterocycloalkenyl radical, an unsubstituted or substituted carbocyclic aryl or heteroaryl radical;

G_3 represents a hydroxyl group protecting group (G_3 defined above) or an acyl radical or an unsubstituted or substituted straight chain or branched alkyl, alkenyl or alkynyl radical, an unsubstituted or substituted cycloalkyl, heterocycloalkyl, cycloalkenyl or heterocycloalkenyl radical, an unsubstituted or

substituted carbocyclic aryl or heteroaryl radical.

DETAILED DESCRIPTION OF THE INVENTION

The new ß-lactams of the formula (IX) herein above are synthesized by modifying the ß-lactams of the formula (XI)

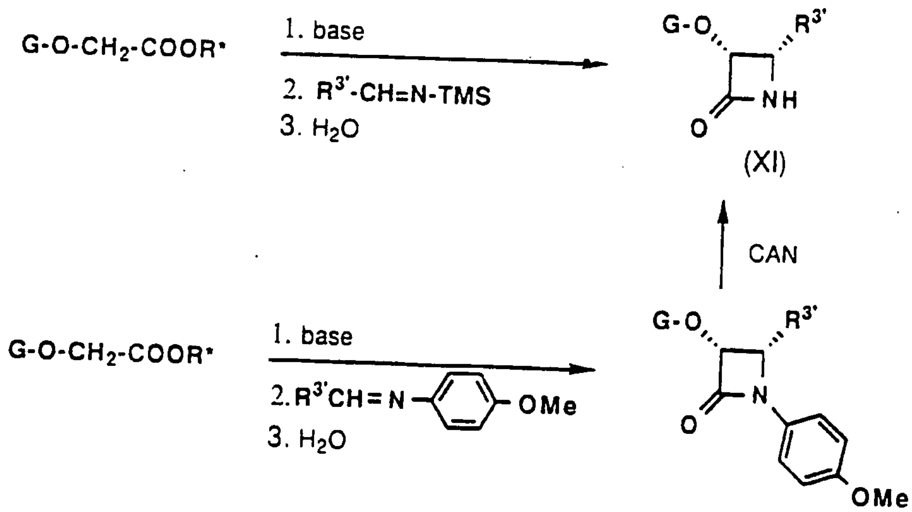


(XI)

wherein G is a hydroxyl protecting group such as triisopropylsilyl (TIPS) and dimethyl(tert-butyl) silyl (TBDMS), and R_3' has been defined hereinabove.

The ß-lactams (XI) are readily prepared by using the chiral enolate - imine cyclocondensation method which has been developed in the present inventor's laboratory as shown in Scheme 1 (Ojima, I. et al., Tetrahedron, 1992, 48, 6985; Ojima, I. et al., J. Org. Chem. 1991, 56, 1681). In this preparation the ß-lactams (XI) with extremely high enantiomeric purities are obtained in high yields. In Scheme 1, R* is a chiral auxiliary moiety which is (-)-trans-2-phenyl-1-cyclohexyl, TMS is a trimethylsilyl radical, and base is lithium diisopropylamide or lithium hexamethyldisilazide; G and R_3' have been defined hereinabove.

Scheme 1



The ß-lactams (XI) are converted to the 3-hydroxy-ß-lactams (XII), followed by protection with ethoxyethyl group (EE) to give the ß-lactams (XIII). The ß-lactams (XIII) are reacted with chloroformates or formic anhydrides or thiocholorformates or thioformic anhydrides in the presence of a base to yield the ß-lactams (XIV) (or thioanalogs thereof) which are used for the coupling with protected 10-deacetylbaccatin III to produce TAXOTÈRE and its analogs. The ß-lactams (XIV) are deprotected under weakly acidic conditions to afford the ß-lactams (XV) which can serve as very useful intermediates to the ß-lactams (XVI) bearing a variety of protecting groups (G_1) at the C-3 position of ß-lactam skeleton. The ß-lactams (XVI) can also be used for the coupling with a protected 10-deacetylbaccatin III to produce Taxotère and its analogs after deprotection.

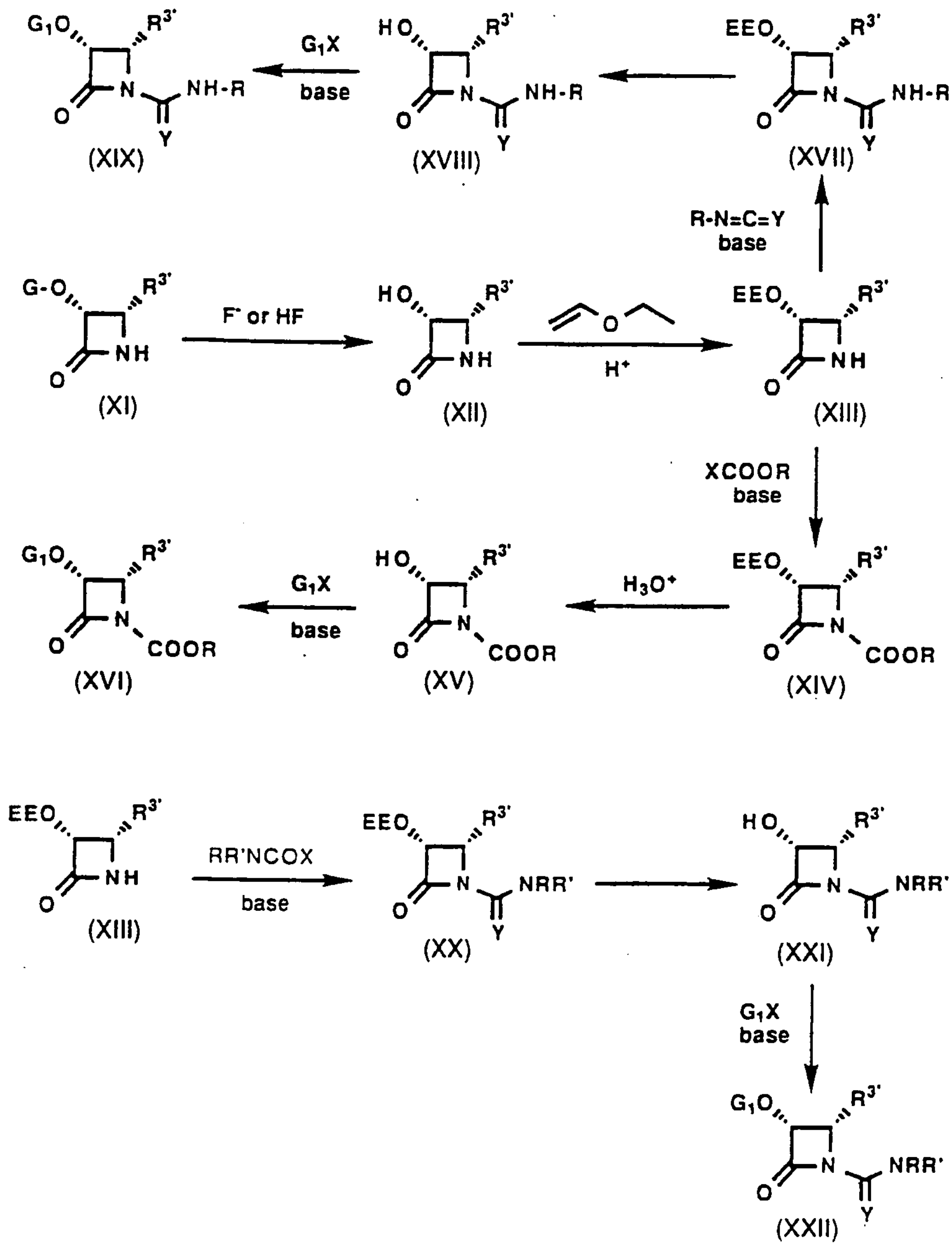
In a similar manner, the ß-lactams (XVII) are prepared by reacting the ß-lactams (XIII) with isocyanates or isothiocyanates in the presence of a base which can be used for the protection of other potent anticancer agents of formula (X) in which R_1 represents RRN-. The ß-lactams (XVII) are deprotected under weakly acidic conditions to give the ß-lactams (XVIII) which can serve as very useful intermediates to a variety of protected 3-hydroxyl-ß-

lactams (XIX). The β-lactams (XVII and XIX) can also be used for the coupling with a protected 10-deacetylbaccatin III to yield a compound of formula (X) in which R_2 represents RR'N- after deprotection.

In a manner similar to that described above, the β-lactams (XX) are prepared by reacting the β-lactams (XIII) with N,N-disubstituted carbamoyl halides in the presence of a base. The β-lactams (XX) are deprotected under weakly acidic conditions to give the 3-hydroxy-β-lactams (XXI), which can serve as very useful intermediates to various protected 3-hydroxy-β-lactams (XXII). The β-lactams (XX and XXII) can readily be used for the coupling with a protected baccatin III to afford a compound of formula (X) after deprotection.

The transformations described above are illustrated in Scheme 2. In Scheme 2, X represents a leaving group such as fluoride, chloride, bromide, iodide, tosylate, mesylate and trifluoromesylate. G_1 represents a group protecting the hydroxyl function selected from methoxylmethyl (MOM), methoxyethyl (MEM), 1-ethoxyethyl (EE), benzyloxymethyl, (β-trimethylsilylethoxyl) methyl, tetrahydropyranyl, 2,2,2-trichloroethoxylcarbonyl (TROC), benzyloxycarbonyl (CBZ), tert-butoxycarbonyl (t-BOC), 9-fluorenyl methoxycarbonyl (FMOC) 2,2,2-trichloroethoxymethyl, trimethyl silyl, dimethyl(t-butyl)silyl, diethylmethylsilyl, dimethyl phenylsilyl and diphenylmethylsilyl, acetyl, chloroacetyl, dichloroacetyl, trichloroacetyl and trifluoroacetyl. $R^{2'}$, $R^{3'}$, R, and R' are defined hereinabove.

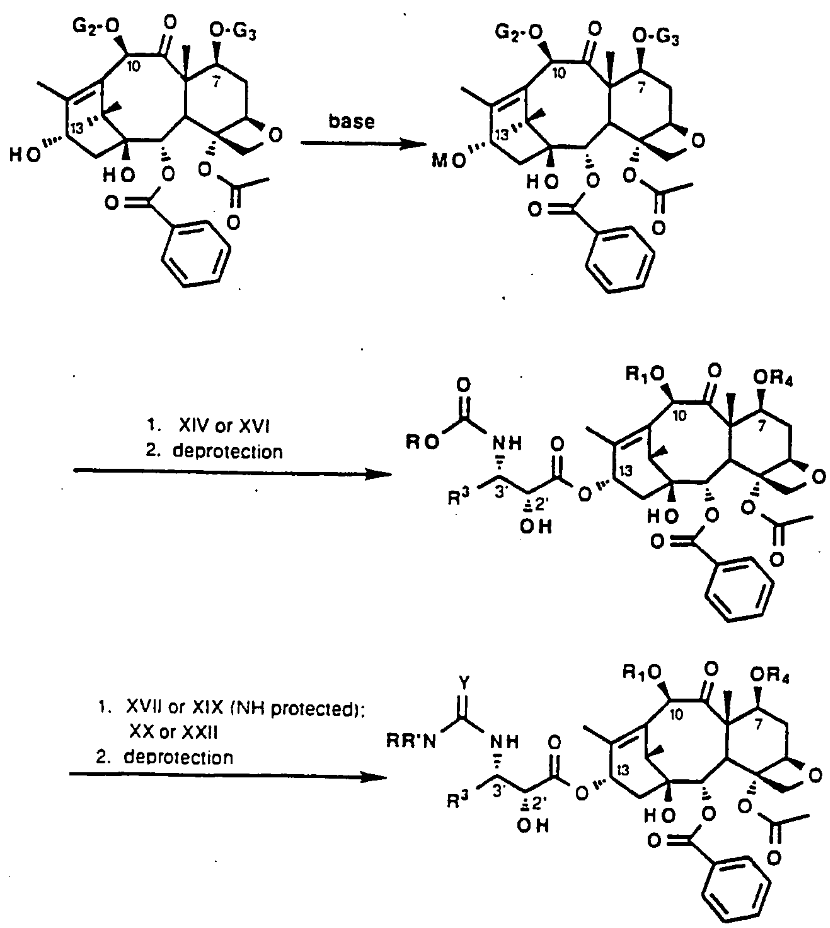
Scheme 2



The ß-lactams (XIV) and (XVI) are readily used for the coupling with protected baccatin IIIs in the presence of base, followed by deprotection to give TAXOTÈRE and its analogs in high yields (Scheme 3). In a similar manner, the ß-lactams (XVII and XIX; with

protection of -NH- moiety) and the ß-lactams (XX and XXII) can be used for the coupling with protected baccatin IIIs, followed by deprotection to give a compound of formula (X) in which R_2 represents $RR^{1'}N$- (Scheme 3).

Scheme 3



G_2 and G_3 represents an hydroxyl protecting group or an acyl radical or an unsubstituted or substituted straight chain or branched alkyl, alkenyl radical, an unsubstituted or substituted cycloalkyl, heterocycloalkyl, cycloalkenyl or heterocycloalkenyl radical, an unsubstituted or substituted carbocyclic aryl or heteroaryl radical.

When G_2 and G_3 are hydroxyl protecting groups [G_1 defined above and 1-ethoxyethoxyl (EE)], these protecting

groups can be attached to the hydroxyl groups of 10-deacetylbaccatin III and its analogs by methods which are generally known to those skilled in the art.

The coupling reaction of the protected baccatin III and the ß-lactam is carried out via an alkali metal or alkaline earth metal alkoxide of the protected baccatin III at the C-13 hydroxyl group. The alkoxide can readily be generated by reacting the protected baccatin III with an alkali metal or alkaline earth metal base such as sodium hexamethyldisilazide, potassium hexamethyldisilazide, lithium hexamethyldisilazide, sodium diisopropylamide, potassium diisopropylamide, lithium diisopropylamide, sodium hydride, potassium hydride, lithium hydride, calcium hydride, magnesium hydride, in a dry nonprotic organic solvent such as tetrahydrofuran (THF), dioxane, ether, dimethoxyethane (DME), diglyme, dimethylformamide (DMF), mixtures of these solvents with hexane, toluene, an xylene, in a preferred temperature range from about -100°C to about 50°C, more preferably at about -78°C to about 25°C. This reaction is preferably carried out under inert atmosphere such as nitrogen and argon. The amount of the base used for the reaction is preferably approximately equivalent to the amount of the protected baccatin III when soluble bases such as sodium hexamethyldisilazide, potassium hexamethyldisilazide, lithium hexamethyldisilazide, sodium diisopropylamide, potassium diisopropylamide, lithium diisopropylamide are used. The use of a slight excess of the base does not adversely affect the reaction. When heterogeneous bases such as sodium hydride and potassium hydride are used, 5-10 equivalents of the base (to the amount of the protected baccatin III) is preferably employed.

The coupling reaction of the metal alkoxide of the protected baccatin III thus generated with the ß-lactam is typically carried out by adding the solution of the ß-lactam in a dry organic solvent exemplified above in

a preferred temperature range from about -100°C to 50°C, more preferably at about -35°C to 25°C. The mixture of reactants is stirred for 15 minutes to 24 hours and the progress and the completion of the reaction is monitored by thin layer chromatography (TLC), for example. When the limiting reactant is completely consumed, the reaction is quenched by addition of a brine. The crude reaction mixture is worked up using the standard isolation procedures which are generally known to those skilled in the art to give the corresponding protected taxoid. The proportion of the ß-lactam and the protected baccatin III is in a range from 2:1 to 1:2, more preferably approximately 1:1 for purposes of economy and efficiency, but the ratio is not critical for the reaction.

The protecting groups, EE, G_1, G_2 and G_3, can then be removed by using the standard procedures which are generally known to those skilled in the art to give the desired taxane derivatives. For example, EE and triethylsilyl groups can be removed with 0.5 N HCl at room temperature for 36 h, and Troc group can be removed with zinc and acetic acid in methanol at 60°C for 1 hour without disturbing the other functional groups and the skeleton of the taxoid.

The following non-limiting examples are illustrative of the present invention. It should be noted that various changes would be made in the above examples and processes therein without departing from the scope of the present invention. For this reason, it is intended that the illustrative embodiments of the present application should be interpreted as being illustrative and not limiting in any sense.

<u>Examples 1-2</u>

(3*R*,4*S*)-3-Triisopropylsilyloxy-4-phenyl-2-azetidinone (1a): To a solution of 645 mL (4.6 mmol) of diisopropylamine in 10 mL of THF, was added 1.85 mL (4.6

mmol, 2.5M) of n-BuLi at 0°C. The solution was stirred 1 h at 0°C followed by the addition of 1.5 g (3.8 mmol) of (-) TIPS ester in 15 mL of THF over a 1 h period (using a cannula) at -78°C. The reaction was stirred 2 h at this temperature followed by the addition of 817 mg (4.6 mmol) of N-TMS benzaldimine in 15 mL of THF over a 2 h period at -95°C. The reaction was stirred overnight at this temperature and allowed to slowly warm up at room temperature. The reaction was quenched by addition of sat. NH_4Cl. The aqueous layer was extracted with ether. The organic layer was washed with 3% HCl and brine, dried over $MgSO_4$ and concentrated. The crude oil was purified by chromatography on silica gel using 1:5 EtAcO/hexanes to give 1.03 g (84%) of ß-lactam as a white solid: Mp 76-77°C; $[\alpha]D^{20}$ +52.7° (C 1.00, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.86-0.93 (m, 21H), 4.81 (d, J = 4.7 Hz, 1H), 5.17 (dd, J = 4.7, 2.6 Hz, 1H), 6.18 (bs, 1H), 7.17-7.35 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$ δ 11.8, 17.4, 17.5, 59.6, 79.9, 127.9, 128.0, 128.1, 136.4, 170.0; IR (KBr) 3234, 2946-2866, 1760, 1458 cm^{-1}. Anal. Calcd for $C_{18}H_{29}NO_2Si$: C 67.66%, H 9.15%, N 4.38%. Found: C 67.64%, H 9.25%, N 4.44%.

In the same manner, ß-lactam **1b** was obtained in good yield.

(3*R*,4*S*)-3-Triisopropylsilyloxy-4-(2-phenylethenyl)-2-azetidinone (1b): 72%; colorless liquid; $_1H$ NMR (300 MHz, $CDCl_3$) δ 0.98-1.02 (m, 21H), 4.36 (dd, J = 4.6, 8.3 Hz, 1H), 5.09 (dd, J = 2.3, 4.6 Hz, 1H), 6.29 (dd, J = 8.3, 16.0 Hz, 1H), 6.59 (d, J = 16.0 Hz, 1H), 6.83, (bs, 1H), 7.23-7.39 (m, 5H); NMR (75 MHz,$CDCl_3$) δ 11.79, 17.61, 17.66, 58.34, 79.86, 126.05, 126.45, 127.90, 128.56, 134.41, 136.30, 169.69; IR (neat) 3262, 3032, 2944, 2865, 1748, 1672, 1623 cm^{-1}. Anal. Calcd for $C_{20}H_{31}NO_2Si$: C, 69.52; H, 9.04; N, 4.05. Found: C, 69.75; H, 9.02; N, 3.89.

Examples 3-4

To a solution of 2.51 mmol of diisopropylamine in 15 mL of THF was added 2.51 mL of n-butyllithium (2.5M in THF) at -10°C. After 30 min, the lithium diisopropylamide (LDA) was generated and the solution was cooled to -95°C. A solution of 2.17 mmol of chiral ester in 5 mL of THF was added. After 1 hr, a solution of 2.5 mmol of the appropriate imine in 3mL of THF was added. The mixture was stirred at -95°C overnight, and the progress of the reaction was monitored by TLC or ^{1}H NMR. The reaction was quenched with sat. NH_4Cl and THF was removed using a rotary evaporator. Ether (10 mL) was added and the aqueous layer was extracted with ether (10 mL x3). Drying and removal of the solvent gave the crude product which was purified by silica gel column chromatography (hexane/ethyl acetate=10:1) to afford the corresponding pure ß-lactam. The enantimeric excess was determined by HPLC using a CHIRALCEL OD column using n-hexane/i-PrOH (90/10) as the eluent.

(3*R*,4*S*)-4-(2-Methylpropyl)-1-(4-methoxyphenyl)-3-triisopropylsilyloxy-2-azetidinone (2a): 87%; pale yellow solid; mp 59-60°C; $[\alpha]D^{20}$ +60.46° (c 1.26, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.96 (d, J = 6.4 Hz, 3H), 1.03 (d, J = 6.4 Hz, 3H), 1.10-1.30 (m, 21H), 1.60-1.68 (m, 1H), 1.70-1.92 (m, 2H), 3.75 (s, 3H), 4.16-4.22 (m, 1H), 5.06 (d, J = 5.1 Hz, 1H), 6.86 (d, J = 9.0 Hz, 2H), 7.32 (d, J = 9.0 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.34, 17.82, 17.91, 22.18, 23.37, 25.34, 35.89, 55.50, 57.33, 76.34, 114.52, 118.73, 131.00, 156.29, 165.58; IR (KBr) 2946, 1742, 1513, 1458, 1249 cm^{-1}. Anal. Calcd for $C_{23}H_{39}NO_3Si$: C, 68.10; H, 9.70; N, 3.45. Found: C, 68.26; H, 9.85; N, 3.35.

(3*R*,4*S*)-4-(Cyclohexylmethyl)-1-(4-methoxyphenyl)-3-triisophropylsilyloxy-2-azetidinone (2b): 83%; low melting point solid; $[\alpha]D^{20}$ +43.7° (c 0.92,

$CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.85-1.95 (m, 34H), 3.78 (s, 3H), 4.19-4.25 (m, 1H), 5.05 (d, J = 5.1 Hz, 1H), 6.86 (d, J = 9.0 Hz, 2H), 7.32 (d, J = 9.0 Hz, 2H); ^{13}C NMR (75 MHz, CDC_{13}) δ 12.15, 17.76, 17.83, 26.12, 26.22, 26.47, 32.84, 34.22, 34.51, 55.36, 56.41, 76.13, 114.30, 118.45, 130.81, 155.99, 165.55; IR (neat) 2925-2865, 1749, 1513, 1464, 1448, 1389, 1246, 1174, 1145, 1128, 939, 882, 828, 684 cm^{-1}. Anal. Calcd for $C_{26}H_{43}NO_3Si$: C, 70.06; H, 9.72; N, 3.14. Found: C, 69.91; H, 9.71; N, 3.02.

Examples 5-6

To a solution of 0.24 mmol of 1-(4-methoxyphenyl)-ß-lactam in CH_3CN (20 mL) was added 0.65 mmol of CAN in 10 mL CH_3CN and 20 mL of water in 20 min at -15°C. After stirring for 1 hr, it was diluted with water (20 mL), and the mixture was then extracted with ethyl acetate (15 mL x2). The combined organic layer was washed with $NaHSO_3$ water (7 mL), 5% (10 mL x 2), 5% Na_2CO_3 (10 mL) and brine (5 mL) in sequence. Drying, removal of the solvent in vacuo followed by decolorization with activated charcoal afforded the crude product. It was further purified by silica gel column chromatography (hexanes/ethyl acetate, 3/1) to furnish N-deprotected ß-lactam.

(3*R*,4*S*)-4-(2-Methylpropyl)-3-triisopropylsilyloxy-2-azetidinone (1c): 83%; yellow oil; $[\alpha]D^{20}$+35.45° (c 1.33, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.93 (d, J = 6.6 Hz, 3H), 0.96 (d, J = 6.6 Hz, 3H), 1.05-1.25 (m, 22H), 1.52 (M, 1H), 1.67 (m, 1H), 3.78 (m, 1H), 4.96 (dd, J = 4.8, 2.4 Hz, 1H), 6.02 (bs, 1H); ^{13}C NMR (75MHz, $CDCl_3$) δ 12.12, 17.72, 17.80, 22.29, 23.08, 25.35, 39.08, 54.45, 78.04, 170.00; IR (neat) 3238, 1759, 1465, 1184 cm^{-1}. Anal. Calcd for $C_{16}H_{33}NO_2Si$: C, 64.16; H, 11.1; N, 4.68. Found: C, 64.17; H, 10.96; N, 4.47.

(3*R*,4*S*)-4-(Cyclohexylmethyl)-3-

triisopropylsilyloxy-2-azetidinone (1d): 85%; yellow oil; $[\alpha]D^{20}$+12.44° (c 1.46, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.97-1.25 (m, 32H), 1.40-1.70 (m, 2H), 3.80 (dt, J = 8.4, 4.8 Hz, 1H), 4.95 (dd, J = 4.8, 2.4 Hz, 1H), 6.05 (bs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.06, 17.77, 17.82, 26.16, 26.25, 26.46, 33.15, 33.82, 34.85, 37.72, 53.89, 77.98, 169.98; IR (neat) 3238, 1759, 1465, 1184 cm^1. Anal. Calcd for $C_{19}H_{37}NO_2Si$: C, 67.20; H, 10.98; N, 4.12. Found: C, 67.40; H, 10.79; N, 3.98.

<u>Examples 7-11</u>

To a solution of 2.6 mmol of 3-triisopropylsilyloxy-4-substituted-2-azetidinone in 20 mL of THF, was added at room temperature 3.1 mmol (1M in THF) of NBu_4F. After 5 h, the solvent was evaporated and the crude oil was directly purified by chromatography on silica gel using 5:1 EtAcO/hexanes to afford of 3-hydroxy-4-substituted-2-azetidinone:

(3*R*,4*S*)-3-Hydroxy-4-phenyl-2-azetidinone (3a): 100%; white solid; mp 189-190°C; $[\alpha]D^{20}$ +181.6° (c 0.5, CH_3OH); ^1H NMR (300 MHz, CD_3OD) δ 4.84 (d, J = 4.7 Hz, 1H), 5.04 (d, J = 4.7 Hz, 1H), 7.25-7.35 (m, 5H); IR (KBr) 3373, 3252, 1732, 1494 cm^{-1}. Anal. Calcd for $C_9H_9NO_2$: C 66.25%, H 5.56%, N 8.58%. Found: C 66.42%, H 5.74%, N 8.62%.

(3*R*,4*S*)-3-Hydroxy-4-(2-phenylethenyl)-2-azetidinone (3b): 82%; white solid; mp 143-144°C; $[\alpha]D^{20}$ +21.9° (c 1.05, MeOH); ^1H NMR (300 MHz, CD_3OD) δ 4.35 (ddd, J = 0.8, 4.7, 7.7 Hz, 1H), 4.93 (d, J = 4.7 Hz, 1H), 6.28 (dd, J = 7.7, 16.0 Hz, 1H), 7.18-7.43 (m, 5H); ^{13}C NMR (75 MHz, CD_3OD) δ 58.95, 79.63, 126.83, 127.58, 128.88, 129.61, 135.28, 137.96, 172.79; IR (KBr) 3320,

3276, 1754, 1464 cm^{-1}. Anal. Calcd for $C_{11}H_{11}NO_2$: C, 69.83; H, 5.86; N, 7.40. Found: C, 69.72; H, 5.92; N, 7.24.

(3*R*,4*S*)-3-Hydroxy-4-(2-methylpropyl)-2-azetidinone (3c): 94%; white solid; mp 141-142°C; $[\alpha]D^{20}$ +26.6° (c 0.70, MeOH); ^{1}H NMR (300 MHz, MeOH-d4) d 0.94 (d, J = 6.8 Hz, 3H), 0.97 (d, J = 6.8 Hz, 3H), 1.45 (m, 2H), 1.71 (sept, J = 6.6 Hz, 1H), 3.75 (m, 1H), 4.79 (d, J = 4.7 Hz, 1H); ^{13}C NMR (75 MHz, MeOH-d4) δ 22.62, 23.48, 26.53, 39.90, 55.47, 77.76, 173.18; IR (KBr) 3274, 3178, 1762, 1685, 1155 cm^{-1}. Anal. Calcd for $C_7H_{13}NO_2$: C, 58.72; H, 9.15; N, 9.78. Found: C, 58.55; H, 9.41; N, 9.69.

(3*R*,4*S*)-4-(Cyclohexylmethyl)-3-hydroxy-2-azetidinone (3d): 92%; white solid; mp 147-148°C; $[\alpha]D^{20}$ + 8.73° (c, 0.573, CH_3OH); ^{1}H NMR (300 MHz, MeOH-d4) δ 0.88-1.82 (m, 13H), 3.78 (m, 1H), 4.79 (d, J = 4.7 Hz, 1H); ^{1}H NMR (300 MHz, DMSO-d6) δ 0.86-1.72 (m, 13H), 3.58 (m, 1H), 4.63 (m, 1H), 5.82 (d, J = 7.6 Hz, 1H), 8.13 (d, J = 5.6, 1H); ^{13}C NMR (75 MHz, MeOH-d4) δ 27.29, 27.41, 27.48, 34.07, 35.06, 36.11, 38.52, 55.02, 77.65, 173.22; IR (KBr) 3301, 3219, 2915, 2847, 1754, 1694, 1168 cm^{-1}. Anal.Calcd for $C_{10}H_{17}NO_2$: C, 65.54, H, 9.35, N, 7.64. Found: C, 65.72, H, 9.46, N, 7.42.

(3*R*,4*S*)-4-cyclohexyl-3-hydroxy-2-azetidinone (3e): A suspension of 500 mg (3.06 mmol) of 4-phenyl-3-hydroxy-2-azetidinone **1a** and 15 mg of Rh-C in 10 mL of methanol was heated at 90°C under 800 psi in an autoclave. After 5 days, the hydrogen pressure was released and the catalyst filtrated on celite. Evaporation of the solvent afforded a solid which was recrystallized in ethyl acetate to give 440 mg (85%) of **3e** as a white solid: White solid; mp 140-140.5°C; $[\alpha]_D^{20}$ + 65.1° (c 0.66, CH_3OH); ^{1}H NMR (250

MHz, MeOH-d_4) δ 0.75-1.10 (m, 2H), 1.12-1.35 (m, 3H), 1.40-2.00 (m, 6H), 3.28 (dd, J = 9.7, 4.6 Hz, 1H), 4.81 (d, J = 4.6 Hz, 1H); ^{1}H NMR (250 MHz, DMSO-d_6) δ 0.75-1.00 (m, 2H), 1.10-1.35 (m, 3H), 1.37-1.55 (m, 1H), 1.58-1.85 (m, 5H), 3.10 (dd, J = 9.6, 4.7 Hz, 1H), 4.67 (m, 1H), 5.87 (d, J = 7.8 Hz, 1H), 8.21 (bs, 1H); ^{13}C NMR (63 MHz, DMSO-d_6) δ 25.08, 25.36, 26.07, 28.83, 29.17, 37.51, 59.04, 76.41, 170.21; IR (KBr) 3312, 3219, 2928, 1726 cm^{-1}. Anal.Calcd for $C_9H_{15}NO_2$: C, 63.88, H, 8.93, N, 8.28. Found: C, 63.70, H, 9.00, N, 8.06.

<u>**Examples 12-16**</u>

To a solution of 1.9 mmol of 3-hydroxy-4-substituted-2-azetidinone in 20 mL of THF, was added at 0°C 3.9 mmol of ethylvinylether. After 2 h, at 0°C, the reaction mixture was diluted with ether and washed with sat. $NaHCO_3$. The organic layer was dried over Na_2CO_3, filtered and concentrated to yield of 3-(1-ethoxyethoxy)-4-substituted-2-azetidinone:

(3*R*,4*S*)-3-(1-Ethoxyethoxy)-4-phenyl-2-azetidinone (4a): 100%; white solid; mp 78-80°C; ^{1}H NMR ($CDCl_3$) δ [0.98 (d, J = 5.4 Hz), 1.05 (d, J = 5.4 Hz), 3H], [1.11 (t, J = 7.1 Hz), 1.12 (t, J = 7.1 Hz), 3H], [3.16-3.26 (m), 3.31-3.42 (m), 3.59-3.69 (m), 2H], [4.47 (q, J=5.4 Hz), 4.68 (q, J = 5.4 Hz), 1H], [4.82 (d, J = 4.7 Hz), 4.85 (d, J = 4.7 Hz), 1H], 5.17-5.21 (m, 1H), 6.42 (bd, 1H), 7.35 (m, 5H); IR (KBr) 3214, 2983, 2933, 1753, 1718, 1456 cm^{-1}. Anal. Calcd for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28; N, 5.95. Found: C, 66.46; H, 7.11; N, 5.88.

(3*R*,4*S*)-3-(1-Ethoxyethoxy)-4-(2-phenylethenyl)-2-azetidinone (4b): 98%; white solid; mp 98-99°C; ^{1}H NMR

(300 MHz, $CDCl_3$) δ [1.17 (t, J = 7.1 Hz), 1.18 (t, J = 7.1 Hz), 3H], [1.26 (d, J = 5.4 Hz), 1.35 (d, J = 5.4 Hz), 3H], [3.44-3.52 (m), 3.60-3.68 (m), 3.75-3.82 (m), 2H], 4.41 (dd, J = 4.9, 8.5 Hz, 1H), [4.81 (q, J = 5.4 Hz), 4.90 (q, J = 5.4 Hz), 1H], [5.11 (d, J = 4.9 Hz), 5.12 (d, J = 4.9 Hz), 1H], 6.01 (bs, 1H), [6.27 (dd, J = 8.5, 15.9 Hz), 6.28 (dd, J = 8.5, 15.9 Hz), 1H], [6.61 (d, J = 15.9 Hz), 6.63 (d, J = 15.9 Hz), 1H], 7.27-7.42 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.04, 20.37, 20.42, 57.22, 57.81, 61.23, 62.22, 78.77, 79.29, 99.50, 99.82, 125.56, 125.79, 126.59, 128.12, 128.65, 134.47, 134.58, 136.15, 168.59, 168.77; IR (KBr) 3310, 3030, 2963, 1770 cm^{-1}. Anal. Calcd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36. Found: C, 69.13; H, 7.44; N, 5.16.

(3*R*,4*S*)-3-(1-Ethoxyethoxy)-4-(2-methylpropyl)-2-azetidinone (4c): 100%; colorless oil: $[\alpha]D^{20}$ +20.93° (c 1.72, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.86 (d, J = 6.5 Hz, 3H), 0.92 (d, J = 6.5 Hz, 3H), 1.17 (t, J = 7.0 Hz, 3H), [1.29 (d, J = 5.3 Hz), 1.34 (d, J = 5.3 Hz), 3H], 1.46 (m, 2H), 1.62 (m, 1H), [3.49 (m), 3.69 (m), 2H)], 3.80 (m, 1H), [4.79 (q, J = 5.4 Hz), 4.90 (q, J = 5,4 Hz), 1H], 4.87 (m, 1H), 6.78 (bs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.08, 20.42, (21.98, 22.06), (23.15, 23.22), 25.35, (39.01, 39.10), (53.35, 53.69), (61.24, 62.24), (77.79, 77.92), (99.75, 100.05), (169.56, 169.65); IR (neat) 3269, 2956, 2871, 1758, 1468, 1382, 1340, 1152, 1115, 1083, 1052, 936, 893 cm^{-1}.

(3*R*,4*S*)-4-(Cyclohexylmethyl)-3-(1-ethoxyethoxy)-2-azetidinone (4d): 100%; colorless oil; $[\alpha]D^{20}$ + 10.92° (c 1.42, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.84-1.71 (m, 13H), 1.16 (t, J = 7.0 Hz, 3H), [1.28 (d, J = 5.3 Hz), 1.33 (d, J = 5.3 Hz), 3H], 3.48 (m, 1H), [3.72 (m), 3.8 (m), 2H], [4.78 (q, J = 5.4 Hz), 4.85 (q, J=5.4 Hz), 1H],

4.82 (m, 1H), 6.76 (bs, 1H); ^{13}C NMR (75 MHz, CDC_{13}) δ 14.37, 19.72, 25.30, 25.44, 25.63, (32.02, 32.13), (33.09, 33.17), (34.03, 34.07), (36.98, 37.07), (52.15, 52.49), (60.49, 61.52), (75.97, 76.39), (99.00, 99.35), (168.98, 169.05); IR (neat) 3278, 2924, 2852, 1758, 1448, 1382, 1150, 1114, 1086, 938, 886 cm^{-1}. Anal. Calcd for $C_{14}H_{25}NO_3$: C,65.85; H, 9.87; N, 5.49. Found: C, 66.03; H, 9.71; N, 5.30.

(3*R*,4*S*)-4-Cyclohexyl-3-(1-ethoxyethoxy)- 2-azetidinone (4e): 100%; white solid; mp 87-89°C; $[\alpha]_D^{20}$ + 83° (c 0.76, CH_3OH); ^1H NMR (250 MHz, $CDCl_3$) δ 0.84 (m, 2H), 1.07-1.34 (m, 9H), 1.66 (m, 6H), 3.32 (m, 1H), [3.42 (q, J = 7.7 Hz), 3.54 (q, J = 7.7 Hz), 3.65 (q, J = 7.7 Hz), 3.74 (q, J = 7.7 Hz), 2H], 4.81 (m, 1H), [4.80 (m), 4.90 (q, J = 5.2 Hz), 1H], 6.92 (bs, 1H); IR ($CHCl_3$) 3412, 2989, 2931, 1760, 1443, 1155, 1114 cm^{-1}. Anal. Calcd for $C_{13}H_{27}NO_3$: C, 64.70; H, 9.61; N, 5.80. Found: C, 64.82; H, 9.66; N, 5.64.

<u>Examples 17-32</u>

To a solution of 2.2 mmol of 3-(1-ethoxyethoxy)-4-substituted-2-azetidinone, 5 mg of DMAP, 4.5 mmol of triethylamine in 20 mL of dichloromethane, was added dropwise at 0°C 3.3 mmol of alkylchloroformate dissolved in 5 mL of dichloromethane. The reaction mixture was stirred overnight at room temperature. The organic layer was washed several times with brine, dried over Na_2CO_3 and concentrated. The crude solid was purified by chromatography on silica gel to yield N-protected β-lactam:

(3*R*,4*S*)-1-Methoxycarbonyl-3-(1-ethoxyethoxy)-

4-phenyl-2-azetidinone (5a): 62%; pale yellow oil; $[\alpha]D^{20}$ +98.2° (c 1.1, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ [0.97 (d, J = 5.4 Hz), 1.08 (d, J = 5.4 Hz), 3H], 1.10 (bt, J = 7.3 Hz, 3H), [3.21 (dq, J = 9.5, 7.1 Hz), 3.32 (q, J = 7.1 Hz), 3.64 (dq, J = 9.5, 7.1 Hz), 2H], [3.76 (s), 3.77 (s), 3H], [4.48 (q, J = 5.4 Hz), 4.69 (q, J = 5.4 Hz), 1H], [5.11 (d, J = 5.9 Hz), 5.14 (d, J = 5.9 Hz), 1H], 5.23 (d, J = 5.9 Hz, 1H), 7.34 (m, 5H); ^{13}C NMR (63 MHz, $CDCl_3$) δ (14.96, 15.07), (19.84, 20.69), 53.59, (60.74, 62.36), (61.14, 61.92), (76.21, 77.21), (99.16, 99.56), (127.73, 128.03, 128.31, 128.36, 128.62, 128.85), (133.41, 133.58), (149.51, 149.57), (165.21, 165.67); IR (neat) 3033, 2979, 2957, 1821, 1738, 1654, 1440, 1336, 1101 cm^{-1}. Anal. Calcd for $C_{15}H_{19}NO_5$: C, 61.42; H, 6.53; N, 4.78. Found: C, 61.55; H, 6.51; N, 4.90.

(3*R*,4*S*)-1-Ethoxycarbonyl-3-(1-ethoxyethoxy)-4-phenyl-2-azetidinone (5b): 82%; colorless oil; $[\alpha]D^{20}$ +100.9° (c 1.08, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ [0.95 (d, J = 5.4 Hz), 1.06 (d, J = 5.4 Hz), 3H], 1.08 (bt, J = 7.3 Hz, 3H), [1.19 (t, J = 7.1 Hz), 1.20 (t, J = 7.1 Hz), 3H], [3.20 (dq, J = 9.4, 7.1 Hz), 3.31 (q, J = 7.1 Hz), 3.32 (q, J = 7.1 Hz), 3.63 (dq, J = 9.4, 7.1 Hz), 2H], [4.18 (q, J = 7.1 Hz), 4.19 (q, J = 7.1 Hz), 2H], [4.47 (q, J = 5.4 Hz), 4.67 (q, J = 5.4 Hz), 1H], [5.09 (d, J = 5.8 Hz), 5.13 (d, J = 5.8 Hz), 1H], 5.21 (d, J = 5.8 Hz, 1H), 7.30 (m, 5H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 14.14, (14.95, 15.07), (19.86, 20.05), (60.76, 62.35), 62.36, (61.14, 61.90), (76.18, 77.20), (99.17, 99.53), (127.73, 128.02, 128.25, 128.30, 128.50, 128.63), (133.59, 133.77), (148.99, 149.05), (165.33, 165.79); IR (neat) 2978, 2934, 1814, 1731, 1646, 1540, 1456, 1323, 1175, 1096 cm^{-1}. Anal. Calcd for $C_{16}H_{21}NO_5$: C, 62.53; H, 6.89; N, 4.56. Found: C, 62.45; H, 6.63; N, 4.83.

(3*R*,4*S*)-1-*n*-Butoxycarbonyl-3-(1-ethoxyethoxy)-4-phenyl-2-azetidinone (5c): 83%; colorless oil; $[\alpha]D^{20}$ +70.4° (c 1.25, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 0.79 (t, J = 7.3 Hz, 3H), [0.94 (d, J = 5.1 Hz), 1.07 (d, J = 5.1 Hz), 3H], 1.07 (t, J = 7.4 Hz, 3H), 1.20 (m, 2H), 1.51 (quint, J = 6.7 Hz, 2H), [3.21 (m), 3.30 (q, J = 7.1 Hz), 3.61 (m), 2H], 4.09 (m, 2H), [4.46 (q, J = 5.2 Hz), 4.66 (q, J = 5.2 Hz), 1H], [5.07 (d, J = 5.8 Hz), 5.11 (d, J = 5.8 Hz), 1H], 5.19 (d, J = 5.8 Hz, 1H), 7.28 (m, 5H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 13.50, (14.95, 15.29), 18.71, (19.84, 20.05), 30.42, (60.77, 62.33), (61.25, 62.02), 66.51, (76.24, 77.26), (99.17, 99.52), (127.76, 128.03, 128.22, 128.27, 128.50, 128.60), (133.61, 133.80), (148.96, 149.02), (165.40, 165.85); IR (neat) 2961, 2933, 1817, 1732, 1653, 1456, 1394, 1250, 1099 cm^{-1}. Anal. Calcd for $C_{18}H_{25}NO_5$: C, 64.46; H, 7.51; N, 4.18. Found: C, 64.44; H, 7.57; N, 4.24.

(3*R*,4*S*)-1-*tert*-Butoxycarbonyl-3-(1-ethoxyethoxy)-4-phenyl-2-azetidinone (5d): 83%; white solid; mp 90-91°C; $[\alpha]D^{20}$ +70.4° (c 1.25, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ [0.96 (d, J = 5.4 Hz), 1.08 (d, J = 5.4 Hz), 3H], [1.09 (t, J = 7.0 Hz), 1.10 (t, J = 7.0 Hz), 3H], [1.36 (s), 1.37 (s), 9H], [3.23 (dq, J = 9.5, 7.1 Hz), 3.32 (q, J = 7.1 Hz), 3.65 (dq, J = 9.5, 7.1 Hz), 2H], [4.48 (q, J = 5.4 Hz), 4.69 (q, J = 5.4 Hz), 1H], [5.03 (d, J = 5.8 Hz), 5.07 (d, J = 5.8 Hz), 1H], 5.18 (d, J = 5.8 Hz, 1H), 7.31 (m, 5H); ^{13}C NMR (63 MHz, $CDCl_3$) δ (14.98, 15.08), (19.89, 20.10), 27.84, (60.74, 62.32), (61.28, 62.08), (75.91, 76.54), 83.48 (99.10, 99.41), (127.76, 128.07, 128.20, 128.42, 128.85), (133.98, 134.16), 147.56, (165.61, 166.04); IR ($CHCl_3$) 3025, 2982, 2932, 1809, 1725, 1601, 1497, 1331, 1256, 1152 cm^{-1}. Anal. Calcd for $C_{18}H_{25}NO_5$: C, 64.46; H, 7.51; N, 4.18. Found: C, 64.50; H, 7.41; N, 4.17.

(3*R*,4*S*)-3-(1-Ethoxyethoxy)-1-phenoxycarbonyl-4-phenyl-2-azetidinone (5e): 79%; white solid; mp 50-52°C; $[\alpha]D^{20}$ +64.9° (c 0.94, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ [1.00 (d, J = 5.3 Hz), 1.11 (m), 3H], [1.14 (m), 3H], [3.27 (m), 3.35 (q, J = 7.1 Hz), 3.70 (m), 2H], [4.54 (q, J = 5.3 Hz), 4.74 (q, J = 5.3 Hz), 1H], [5.25 (d, J = 5.8 Hz), 5.29 (d, J = 5.8 Hz), 1H], 5.34 (d, J = 5.8 Hz, 1H), 7.03-7.39 (m, 10H); IR ($CHCl_3$) 3028, 2981, 2934, 1815, 1744, 1591, 1486, 1327, 1192 cm^{-1}. Anal. Calcd for $C_{20}H_{21}NO_5$: C, 67.59; H, 5.96; N, 3.94. Found: C, 67.33; H, 6.06; N, 3.75.

(3*R*,4*S*)-3-(1-Ethoxyethoxy)-4-phenyl-1-phenyl methoxycarbonyl-2-azetidinone (5f): 44%; white solid; mp 58-60°C; $[\alpha]D^{20}$ +91.4° (c 1.16, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ [0.97 (d, J = 5.3 Hz), 1.09 (d, J = 5.3 Hz), 3H], [1.10 (t, J = 7.0 Hz), 1.11 (t, J = 7.0 Hz), 3H], [3.23 (dq, J = 9.5, 7.1 Hz), 3.33 (q, J = 7.1 Hz), 3.66 (dq, J = 9.5, 7.1 Hz), 2H], [4.50 (q, J = 5.4 Hz), 4.70 (q, J = 5.4 Hz), 1H], [5.13 (d, J = 5.6 Hz), 5.15 (d, J = 5.6 Hz), 1H], [5.19 (s), 5.20 (s), 2H], 5.23 (d, J = 5.6 Hz, 1H), 7.21 (m, 2H), 7.26-7.37 (m, 8H); ^{13}C NMR (63 MHz, $CDCl_3$) δ (14.99, 15.10), (19.90, 20.10), (60.83, 62.41), (61.64, 62.14), 68.01, (76.31, 77.28), (99.19, 99.53), (127.37, 127.86, 128.07, 128.16, 128.36, 128.52, 128.63, 128.85), (133.49, 133.68), 134.89, (148.72, 148.78), (165.37, 165.81); IR ($CHCl_3$) 3028, 2981, 2934, 1815, 1733, 1604, 1450, 1380, 1004 cm^{-1}. Anal. Calcd for $C_{21}H_{23}NO_5$: C, 68.28; H, 6.28; N, 3.79. Found: C, 68.07; H, 6.43; N, 3.72.

(3*R*,4*S*)-1-*tert*-Butoxycarbonyl-4-cyclohexyl-3-(1-ethoxyethoxy)-2-azetidinone (5g): 91%; colorless oil; $[\alpha]_D^{20}$ +62.5° (c 1.12, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 1.10-1.28 (m, 6H), 1.15 (t, J = 7.0 Hz, 3H), [1.27 (d, J =

5.4 Hz), 1.31 (d, J = 5.4 Hz), 3H], [1.45 (s), 1.46 (s), 9H], 1.63-1.70 (m, 5H), [3.43 (dq, J = 9.2, 7.0 Hz), 3.62 (m), 3.75 (d, J = 7.0 Hz), 3.78 (d, J = 7.0 Hz), 2H], 3.85 (t, J = 6.1 Hz, 1H), [4.78 (q, J = 5.4 Hz), 4.88 (m), 1H], [4.85 (d, J = 6.1 Hz), 4.86 (d, J = 6.1 Hz), 1H]; ^{13}C NMR (63 MHz, $CDCl_3$) δ 15.07, (20.25, 20.37), (26.05, 26.14), 26.26, (27.33, 27.95), (29.05, 29.20), (30.04, 30.23), (37.54, 37.64), (61.19, 62.53), (62.06, 62.32), (75.42, 75.85), 83.06, 100.11, 148.72, (166.70, 166.76); IR (neat) 2980, 2931, 2854, 1807, 1725, 1450, 1370, 1329, 1212, 1118 cm^{-1}. Anal. Calcd for $C_{18}H_{31}NO_5$: C, 63.32; H, 9.15; N, 4.10. Found: C, 63.15; H, 8.97; N, 3.96.

(3*R*,4*S*)-1-*tert*-Butoxycarbonyl-3-(1-ethoxy ethoxy)-4-(2-phenylethenyl)-2-azetidinone (5h): 86%; white solid; mp 69-73°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ [1.16 (t, J = 7.1 Hz), 1.18 (t, J = 7.1 Hz), 3H], [1.25 (d, J = 5.4 Hz), 1.36 (d, J = 5.4 Hz), 3H], 1.48 (s, 9 H), [3.47 (m), 3.62 (m), 3.80 (m), 2H], 4.68 (dd, J = 5.8, 8.8 Hz, 1H), [4.82 (q, J = 5.4 Hz), 4.91 (q, 5.4 Hz), 1H], [5.09 (d, J = 5.8 Hz), 5.11 (d, J = 5.8 Hz), 1H], [6.23 (dd, J = 8.8, 15.8 Hz), 6.25 (dd, J = 8.8, 15.8 Hz), 1H], [6.72 (d, J = 15.8 Hz), 6.73 (d, J = 15.8 Hz), 1H], 7.27-7.44 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.98, 20.31, 27.98, 60.24, 60.85, 61.46, 62.36, 63.58, 83.38, 99.63, 99.87, 122.45, 122.63, 126.69, 128.20, 128.61, 136.15, 136.34, 136.38, 147.74, 147.79, 165.33, 165.53; IR (KBr) 3027, 3020, 2984, 2933, 1809, 1723 cm^{-1}. Anal. Calcd for $C_{20}H_{27}NO_5$: C, 66.46; H, 7.53; N, 3.88. Found: C, 66.60; H, 7.50; N, 3.87.

(3*R*,4*S*)-1-*tert*-Butoxycarbonyl-3-(1-ethoxy ethoxy)-4-(2-methylpropyl)-2-azetidinone (5i): 80%; yellow oil; $[\alpha]D^{20}$ +77.45° (c 0.216, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89 (d, J = 5.7 Hz, 6H), 1.41 (t, J = 7.1

Hz, 3H), [1.25 (d, J = 5.3 Hz), 1.31 (d, J = 5.3 Hz), 3H], 1.45 (s, 9H), 1.51-1.67 (m, 3H), [3.48 (dq, J = 9.3, 7.1 Hz), 3.55-3.71 (m, 1H), 3.80 (dq, J = 9.3, 7.1 Hz), 2H], 4.08 (q, J = 6.1 Hz, 1H), [4.70 (q, J = 5.3 Hz), 4.90 (q, J = 5.3 Hz), 1H], 4.85 (d, J = 6.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.95, (20.11, 20.28), (22.42, 22.59), 22.70, (24.89, 25.07), 27.83, (37.03, 37.31), (56.14, 56.38), (61.07, 62.27), (75.65, 75.92), 82.98, 99.91, 148.1, (166.1, 165.9); IR (neat) 2931, 2960, 2872, (1790, 1807), (1708, 1726), (1454, 1465), 1332, 1256, 1048, 1158, 996, 955, 857, 834, 770 cm^{-1}. Anal. Calcd for $C_{16}H_{26}NO_5$: C, 60.93; H, 9.27; N, 4.44. Found: C, 61.19; H, 9.41; N, 4.37.

(3*R*,4*S*)-1-*tert*-Butoxycarbonyl-4-cyclohexyl methyl-3-(1-ethoxyethoxy)-2-azetidinone (5j): 93%; yellow oil; $[\alpha]D^{20}$ +75.64° (c 0.78, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.81-1.74 (m, 13H), 1.19 (t, J = 7.1 Hz, 3H), 1.48 (s, 9H), [1.30 (d, J = 5.3 Hz), 1.35 (d, J = 5.3 Hz), 3H], [3.45 (dq, J = 9.3, 7.1 Hz), 3.62-3.71 (m), 3.78 (dq, J = 9.3, 7.1Hz), 2H], 4.01 (m, 1H), [4.81 (q, J = 5.3 Hz), 4.91 (q, J = 5.3 Hz), 1H], [4.86 (d, J = 6.1 Hz), 4.87 (d, J = 6.1 Hz), 1H]; ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.03, 20.19, 20.36, 26.10, 26.36, 27.91, (33.17, 33.31), (33.35, 33.49), (34.33, 34.58), (35.39, 35.68), (55.77, 55.99), (61.14, 62.21), (75.74, 75.90), 82.96, (99.86, 99.95), 147.96, 166.13; IR (neat) 2979, 2923, 2850, 1719, 1807, 1449, 1336, 1154 cm^{-1}. Anal. Calcd. for $C_{19}H_{33}NO_5$: C, 64.20; H, 9.36; N,3.94. Found: C, 64.00; H, 9.17; N, 4.02.

Examples 28-32

To a solution of 0.5 mmol of 3-(1-ethoxyethoxy)-4-phenyl-

2-azetidinone in 6 mL of tetrahydrofuran, was added dropwise at -78°C 0.6 mmol of n-BuLi. After 5 min, 1 mmol of an isocyanate or an isothiocyanate was added. The reaction mixture was stirred 30 min at -78°C and quenched by addition of 2 mL sat. NH_4Cl solution. The reaction mixture was diluted with 30 mL of ether and the organic layer was washed several times with brine, dried over Na_2CO_3 and concentrated. The crude solid was purified by chromatography on silica gel to yield N-protected β-lactam:

(3*R*,4*S*)-3-(1-Ethoxyethoxy)-1-phenylcarbamoyl-4-phenyl-2-azetidinone (7a): 66%; pale yellow solid; mp 152-155°C; $[\alpha]D^{20}$ +87.8° (c 0.9, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ [1.07 (d, J = 5.4 Hz), 1.13 (d, J = 5.4 Hz), 3H], 1.16 (t, J = 7.1 Hz, 3H), [3.26 (dq, J = 9.5, 7.1 Hz), 3.37 (q, J = 7.1 Hz), 3.39 (q, J = 7.1Hz), 3.67 (dq, J = 9.5, 7.1 Hz), 2H], [4.53 (q, J = 5.4 Hz), 4.72 (q, J = 5.4 Hz), 1H], 5.28 (m, 2H), [6.59 (bs), 6.60 (bs), 1H], 7.10-7.55 (m, 10H), 8.68 (bs, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) δ (15.04, 15.16), (19.98, 20.11), (60.99, 62.53), 61.80, (76.05, 76.66), (99.34, 99.70), (119.63, 120.69, 124.37, 127.67, 127.95, 128.40, 128.45, 128.67, 128.85, 129.04, 129.12, 130.49), 133.48, (137.03, 137.28), (147.23, 147.29), (168.12, 168.52); IR ($CHCl_3$) 3342, 3017, 2982, 2932, 1773, 1719, 1602, 1548, 1445, 1312, 1224, 1210 cm^{-1}. Anal. Calcd for $C_{20}H_{22}N_2O_4$: C, 67.78; H, 6.26; N, 7.90. Found: C, 67.92; H, 5.98; N, 8.17.

(3*R*,4*S*)-1-*tert*-Butylcarbamoyl-3-(1-ethoxy ethoxy)-4-phenyl-2-azetidinone (7b): 74%; pale yellow viscous oil; $[\alpha]D^{20}$ +144.3° (c 0.7, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ [0.96 (d, J = 5.3 Hz), 1.05 (d, J = 5.3 Hz), 3H], 1.10 (t, J = 7.1 Hz, 3H), [1.33 (s), 1.34 (s), 9H], [3.21 (dq, J = 9.3, 7.0 Hz), 3.30 (q, J = 7.0 Hz), 3.33

(q, J = 7.1Hz), 3.62 (dq, J = 9.1, 7.0 Hz), 2H], [4.46 (q, J = 5.4 Hz), 4.66 (q, J = 5.4 Hz), 1H], 5.10-5.19 (m, 2H), [6.59 (bs), 6.60 (bs), 1H], 7.23-7.36 (m, 5H); ^{13}C NMR (63 MHz, $CDCl_3$) δ (14.86, 14.99), (19.75, 19.95), (28.81, 29.30), (60.62, 61.20), (60.80, 62.29), (75.57, 76.76), (98.91, 99.34), (127.07, 127.40, 127.70, 128.17, 128.29, 128.53), (133.71, 133.86), (148.54, 148.59), (167.67, 168.13); IR ($CHCl_3$) 3362, 3035, 2977, 2932, 1767, 1710, 1605, 1537, 1457, 1366, 1320, 1282, 1217, 1100 cm^{-1}. Anal. Calcd for $C_{18}H_{26}N_2O_4$: C, 64.65; H, 7.84; N, 8.38. Found: C, 64.46; H, 7.75; N, 8.39.

(3*R*,4*S*)-1-Benzylcarbamoyl-3-(1-ethoxy ethoxy)-4-phenyl-2-azetidinone (7c): 50%; pale yellow viscous oil; [α]D^{20} +66.2° (c 0.8, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ [0.99 (d, J = 5.5 Hz), 1.08 (d, J = 5.5 Hz), 3H], 1.12 (m, 3H), [3.16-3.40 (m), 3.63 (m), 2H], [4.35-4.55 (m), 4.69 (q, J = 5.5 Hz), 3H], 5.21 (m, 2H), [7.03 (bs), 7.05 (bs), 1H], 7.32 (m, 10H); ^{13}C NMR (63 MHz, $CDCl_3$) δ (15.01, 15.14), (19.90, 20.11), 43.83, (60.66, 62.44), (60.75, 61.54), (75.93, 77.04), (99.16, 99.56), (127.25, 127.64, 127.69, 128.17, 127.93, 128.35, 128.55, 128.64, 128.74), (133.59, 133.76), 137.80, 150.02, (167.73, 168.19); IR ($CHCl_3$) 3379, 3090, 3033, 2980, 2930, 1773, 1707, 1604, 1536, 1455, 1319, 1270, 908 cm^{-1}. Anal. Calcd for $C_{21}H_{24}N_2O_4$: C, 68.46; H, 6.57; N, 7.60. Found: C, 68.30; H, 6.66; N, 7.51.

(3*R*,4*S*)-3-(1-Ethoxyethoxy)-1-ethylcarbamoyl-4-phenyl-2-azetidinone (7d): 63%; pale yellow oil; [α]D^{20} +96.7° (c 0.9, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) d [0.96 (d, J = 5.3 Hz), 1.04 (d, J = 5.3 Hz), 3H], 1.05-1.18 (m, 3H), [3.13-3.39 (m), 3.59 (m), 4H], [4.45 (q, J = 5.3 Hz), 4.65 (q, J = 5.3 Hz), 1H], 5.16 (m, 2H), [6.60 (bs), 6.62 (bs), 1H], 7.27 (m, 5H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 14.98, (19.84,

29.93), 34.79, (60.56, 61.35), (60.72, 62.35), (75.91, 77.03), (99.14, 99.54), (127.28, 127.55, 127.85, 128.27, 128.40), (133.74, 133.89), (149.87, 149.93), (167.62, 168.07); IR ($CHCl_3$) 3378, 3035, 2980, 2934, 1774, 1704, 1537, 1455, 1321, 1271, 1112, 1025 cm^{-1}.

(3*R*,4*S*)-3-(1-Ethoxyethoxy)-1-phenylthio carbamoyl-4-phenyl-2-azetidinone (7e): 82%; yellow solid; mp 108-112°C; $[\alpha]D^{20}$ +68° (c 1.14, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ [1.02 (d, J = 5.5 Hz), 1.11 (d, J = 5.5 Hz), 3H], 1.16 (t, J = 7.3 Hz, 3H), [3.20-3.44 (m), 3.66 (dq, J = 9.4, 7.3 Hz), 2H], [4.52 (q, J = 5.5 Hz), 4.72 (q, J = 5.5 Hz), 1H], [5.30 (d, J = 5.5 Hz), 5.32 (d, J = 5.5 Hz), 1H], [5.49 (d, J = 5.5 Hz), 5.52 (d, J = 5.5 Hz), 1H], 7.36 (m, 8H), 7.67 (d, J = 7.8 Hz, 2H), 10.37 (bs, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) δ (15.04, 15.17), (19.95, 20.13), (60.96, 62.57), (63.92, 64.75), (74.75, 75.84), (99.34, 99.68), (123.43, 126.58, 127.91, 128.28, 128.49, 128.86, 128.91), (133.10, 133.25), (137.36), (166.55, 166.52), (174.812); IR ($CHCl_3$) 3288, 3024, 2983, 1760, 1497, 1385, 1222 cm^{-1}.

<u>Examples 33-34</u>

(3*R*,4*S*) -1-Morpholinecarbonyl-3-(-1-ethoxyethoxy)-4-phenyl-2-azetidinone (7f): To a solution of 30 mg (0.13 mmol) of 3-(1-ethoxyethoxy)-4-phenyl-2-azedinone 6 in 2 mL of CH_2Cl_2, 2 mg of DMAP and 0.05 mL of triethylamine was added at room temperature. After 5 min. 22.9 mg (0.15 mmol) of morpholinecarbonyl chloride was added. The reaction mixture was stirred for 2h at room temperature. The reaction mixture was diluted with 20 mL of CH_2Cl_2 and the organic layer was washed two times with brine, dried over Na_2CO_3 and concentrated. The crude solid product was purified by chromatography on silica gel to yield pure 7f: 87%; pale yellow oil; ^1H NMR (250 MHz,

$CDCl_3$) δ [0.90 (d, J = 5.3 Hz), 1.01 (d, J = 5.3 Hz) (3H)], [1.04 (t, J = 7.1 Hz), 1.18 (t, J = 7.1 Hz)] (3H), 3.20 (m, 4H), [3.28 (m), 3.53 (m), 3.67 (m), (2H)], 3.60 (m, 4H), [4.41 (q, J = 5.3 Hz), 4.63 (q, J = 5.3 Hz) (1H), [5.07 (d, J = 5.8 Hz), 5.08 (d, J = 5.8 Hz) (1H), [5.29 (d, J = 5.8 Hz), 5.32 (d, J = 5.8 Hz) (1H)], 7.23-7.27 (m, 5H).

Examples 35-53

To a solution of 0.37 mmol of O-EE β-lactam in 4 mL THF was added 4 mL of 0.5 N HCl. The completion of reaction was monitored by TLC. After 1-3 hr, the reaction mixture was concentrated in vacuo to remove THF. The residue was dissolved in 30 mL ether and washed with 10 mL saturated $NaHCO_3$ solution. The ether layer was washed with brine, dried over anhydrous sodium sulfate, and concentrated in vacuo to give 3-hydroxy β-lactam:

(3*R*,4*S*)-3-Hydroxy-1-methoxycarbonyl-4-phenyl-2-azetidinone (6a): 66%; white solid; mp ; 91-92°C $[\alpha]D^{20}$ +108° (c 0.63, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 3.80 (s, 3H), 5.13 (d, J = 6.0 Hz, 1H), 5.22 (d, J = 6.0 Hz, 1H), 7.25-7.42 (m, 5H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 53.77, 61.44, 77.33, 127.16, 128.94, 132.65, 149.20, 166.04; IR ($CHCl_3$) 3432, 3024, 2996, 1806, 1730, 1440, 1333, 1188 cm^{-1}. MS(FAB) m/z (%) 222 (M+1, 38), 194(29), 164(100).

(3*R*,4*S*)-1-Ethoxycarbonyl-3-hydroxy-4-phenyl-2-azetidinone (6b): 59%; white solid; mp 112-113°C; $[\alpha]D^{20}$ +181° (c 0.97, CHCl3); ^1H NMR (250 MHz, $CDCl_3$) δ 1.27 (t, J = 7.1 Hz, 3H), 4.25 (q, J = 7.1 Hz, 2H), 5.14 (d, J = 6.0 Hz, 1H), 5.22 (d, J = 6.0 Hz, 1H), 7.27-7.39 (m, 5H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 14.08, 61.36, 63.00, 77.26, 127.08, 128.83, 132.75, 149.08, 165.79; IR ($CHCl_3$)

3605, 3017, 2985, 1815, 1732, 1684, 1396, 1373, 1268, 1020 cm^{-1}; MS (FAB) m/z (%) 236 (M+1,98), 208(23), 178(100).

(3*R*,4*S*)-1-*n*-Butoxycarbonyl-3-hydroxy-4-phenyl-2-azetidinone (6c): 69%; white solid; mp 88-89°C; $[\alpha]D^{20}$ +159.1° (c 0.71, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 0.78 (t, J = 7.3 Hz, 3H), 1.14 (m, 2H), 1.50 (m, 2H), [4.07 (q, J = 8.9 Hz), 4.10 (q, J = 8.9 Hz), 2H), 5.05 (d, J = 5.9 Hz, 1H), 5.11 (d, J = 5.9 Hz, 1H), 7.22-7.36 (m, 5H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 13.44, 18.71, 30.44, 61.54, 66.72, 77.31, 127.21, 128.80, 132.89, 149.15, 166.06; IR ($CHCl_3$) 3562, 3018, 2962, 1813, 1730, 1456, 1395, 1324, 1222, 1099 cm^{-1}. MS (FAB) m/z (%) 264(M+1,62), 236(20), 208(40), 206(100).

(3*R*,4*S*)-1-*tert*-Butoxycarbonyl-3-hydroxy-4-phenyl-2-azetidinone (6d): 88%; white solid; mp 131.5-132°C; $[\alpha]D^{20}$ +173.5° (c 0.98, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 1.40 (s, 9H), 2.70 (bs, 1H), 5.08 (d, J = 5.9 Hz, 1H), 5.14 (d, J = 5.9 Hz, 1H), 7.27 (d, J = 6.1 Hz, 2H), 7.38 (m, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 27.87, 61.56, 77.00, 83.85, 127.20, 128.77, 128.82, 133.13, 147.72, 169.49; IR ($CHCl_3$) 3616, 3019, 2976, 1807, 1726, 1601, 1522, 1422, 1333, 1212, 1152 cm^{-1}. Anal. Calcd for $C_{14}H_{17}NO_4$: C, 63.87; H, 6.51; N, 5.32. Found: C, 63.71; H, 6.38; N, 5.12.

(3*R*,4*S*)-3-Hydroxy-1-phenoxycarbonyl-4-phenyl-2-azetidinone (6e): 72%; white solid; mp 125-126°C; $[\alpha]D^{20}$ +107° (c 1.45, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 5.21 (d, J = 6.1 Hz, 1H), 5.34 (d, J = 6.1 Hz, 1H), 7.07-7.45 (m, 10H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 61.83, 73.24, 121.15, 125.46, 126.80, 127.22, 128.09, 128.80, 129.11, 129.30, 132.40, 138.49, 154.05; IR ($CHCl_3$) 3615, 3020, 2976, 1821, 1740, 1506, 1487, 1332, 1219 cm^{-1}.

(3*R*,4*S*)-1-Benzyloxycarbonyl-3-hydroxy-4-phenyl-2-azetidinone (6f): 85%; white solid; mp 105-106°C; $[\alpha]D^{20}$ +177° (c 0.6, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 5.12 (d, J = 6.2 Hz, 1H), 5.22 (m, 3H), 7.24-7.40 (m, 10H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 61.53, 68.30, 77.43, 127.19, 128.13, 128.58, 129.06, 132.55, 134.74, 148.90, 165.92; IR ($CHCl_3$) 3557, 3018, 2924, 1814, 1731, 1383, 1273, 1162, 1004 cm^{-1}. MS (FAB) m/z (%) 298(M+1,14), 273(4).

(3*R*,4*S*)-1-tert-Butoxycarbonyl-4-cyclohexyl-3-hydroxy-2-azetidinone (6g): 96%; white solid; mp 121-122°C; $[\alpha]D^{20}$+78° (c 0.68, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 1.17-1.75 (m, 11H), 1.48 (s, 9H), 3.83 (t, J+6.5 Hz, 1H), 4.96 (d, J=6.5 Hz, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 25.87, 25.99, 26.24, 27.96, 29.69, 29.90, 37.45, 63.30, 75.24, 83.43, 148.80, 168.60; IR ($CHCl_3$) 3354, 2931, 2848, 1801, 1724, 1324, 1154 cm^{-1}.

(3*R*,4*S*)-1-*tert*-Butoxycarbonyl-3-hydroxy-4-(2-phenylethenyl)-2-azetidinone (6h): 96%; white solid; mp 132-133°C; $[\alpha]D^{20}$ +122.0° (c 1.1, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 1.47 (s, 9H), 3.88 (bs, 1H), 4.71 (dd, J = 4.8, 8.0 Hz, 1H), 5.07 (d, J = 4.8 Hz, 1H), 6.26 (dd, J = 8.0, 15.9 Hz, 1H), 6.72 (d, J = 15.9 Hz, 1H), 7.24-7.43 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.94, 60.78, 76.58, 83.77, 121.41, 126.75, 128.26, 128.59, 135.94, 136.62, 147.85, 166.95; IR (KBr) 3242, 3039, 2954, 1812, 1726 cm^{-1}. Anal. Calcd for $C_{16}H_{19}NO_4$: C, 66.42; H, 6.62; N, 4.84. Found: C, 66.31; H, 6.71; N, 4.76.

(3*R*,4*S*)-1-*tert*-Butoxycarbonyl-3-hydroxy-4-(2-methylpropyl)-2-azetidinone (6i): 98%; pale yellow solid; mp 108°C; $[\alpha]D^{20}$ +76.14° (c 0.88, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.93 (d, J = 6.3 Hz, 6H), 1.48 (s, 9H),

1.62-1.82 (m, 3H), 4.12 (m, 1H), 4.30 (bs, 1H), 4.93 (d, J = 5.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.45, 22.78, 25.12, 27.96, 36.28, 57.59, 75.39, 83.46, 148.13, 168.00; IR (KBr) 3363, 2960, 2926, 1733, 1763, 1458, 1370, 1350, 1303, 1153 cm^{-1}. Anal. Calcd. for $C_{12}H_{21}NO_4$: C, 59.24; H, 8.70; N, 5.76. Found: C, 59.47; H, 8.91; N, 5.51.

(3*R*,4*S*)-1-*tert*-Butoxycarbonyl-4-cyclohexylmethyl-3-hydroxy-2-azetidinone (6j): 100%; white solid; mp 105-106°C; [α]D^{20} +61.89° (c 0.74, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.82-1.84 (m, 13H), 1.50 (s, 9H), 3.82 (bs, 1H), 4.14 (m, 1H), 4.93 (d, J = 5.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.12, 26.17, 26.42, 33.20, 33.47, 33.59, 34.71, 28.00, 57.13, 75.49, 83.47, 148.08, 167.57; IR (KBr) 3442, 2921, 2850, 1797, 1682, 1447, 1354, 1342, 1159 cm^{-1}. Anal. Calcd. for $C_{15}H_{25}NO_4$: C, 63.58; H, 8.89; N, 4.94. Found: C, 63.76; H, 8.72; N, 4.68.

(3*R*,4*S*)-3-hydroxy-4-phenyl-1-phenylcarbamoyl-2-azetidinone (8a): 88%; white solid; mp 197-200°C; [α]D^{20} +206.4° (c 1.26, $CHCl_3$); ^{1}H NMR (250 MHz, CD_3COCD_3) δ 5.39-5.47 (m, 2H), 7.07-7.60 (m, 10H), 8.80 (bs, 1H); ^{13}C NMR (63 MHz, CD_3COCD_3) δ 61.98, 78.06, 119.85, 124.31, 128.11, 128.31, 128.60, 129.48, 135.31, 138.43, 148.17, 169.76; IR ($CHCl_3$) 3343, 3018, 2975, 1772, 1712, 1603, 1548, 1447, 1362, 1219, 1045 cm^{-1}; MS (FAB) m/z(%) 283(2), 263 (33) 207(22), 143(100).

(3*R*,4*S*)-1-*tert*-Butylcarbamoyl-3-hydroxy-4-phenyl-2-azetidinone (8b): 89%; white solid; mp 148-151°C; [α]D^{20} +160.9° (c 1.28, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.35 (s, 9H), 3.16 (bs, 1H), 4.97 (d, J = 5.5 Hz, 1H), 5.11 (d, J = 5.5 Hz, 1H), 6.60 (bs, 1H), 7.19-7.38 (m, 5H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 28.84, 51.53, 60.74, 76.61, 127.00, 128.61, 128.70, 133.13, 148.78, 168.30; IR

($CHCl_3$) 3362, 3018, 2975, 1767, 1710, 1533, 1422, 1318, 1216, 1045 cm^{-1}. Anal. Calcd for $C_{14}H_{18}N_2O_3$: C, 64.11; H, 6.92; N, 10.68. Found: C, 64.10; H, 7.08; N, 10.49.

(3*R*,4*S*)-1-Benzylcarbamoyl-3-hydroxy-4-phenyl-2-azetidinone (8c): 63%; white solid; mp 165-168°C; $[\alpha]D^{20}$ +139° (c 0.64, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 3.10 (bs, 1H), 4.43 (dd, J = 15.2, 5.8 Hz, 1H), 4.50 (dd, J = 15.2, 5.8 Hz, 1H), 5.03 (d, J = 5.6 Hz, 1H), 5.20 (d, J = 5.6 Hz, 1H), 7.06 (t, J = 5.8 Hz, 1H), 7.23-7.33 (m, 10H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 43.79, 61.01, 76.94, 127.13, 127.73, 128.80, 128.86, 132.94, 137.59, 150.15, 168.34; IR ($CHCl_3$) 3364, 3028, 2925, 1771, 1704, 1537, 1455, 1361, 1219, 1190, 987 cm^{-1}. Anal. Calcd for $C_7H_{16}N_2O_3$: C_1 68.91; H, 5.44; N. 9.45. Found: C_1 68.89; H. 5.66; N, 9.34.

(3*R*,4*S*)-1-Ethylcarbamoyl-3-hydroxy-4-phenyl-2-azetidinone (8d): 55%; white solid; mp 141- 42°C; $[\alpha]D^{20}$ +211.4° (c 0.44, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 1.19 (t, J = 7.2 Hz, 3H), 3.34 (qd, J = 7.2, 1.6 Hz, 2H), 5.09 (d, J = 5.6 Hz, 1H), 5.27 (d, J = 5.6 Hz, 1H), 6.63 (bt, J = 1.6 Hz, 1H), 7.23-7.44 (m, 5H); ^{13}C NMR (63 MHz, $CDCl_3$) d 15.04, 34.94, 60.77, 76.98, 127.00, 128.92, 129.06, 132.83, 149.96, 167.98; IR ($CHCl_3$) 3381, 3018, 2990, 1770, 1732, 1651, 1589, 1422, 1298, 1210, 1045 cm^{-1}.

(3*R*,4*S*)-3-(1-Hydroxy)-1-phenylthiocarbamoyl-4-phenyl-2-azetidinone (8e): 78%; yellow solid; mp 85-88°C; $[\alpha]D^{20}$ + 156.7° (c 0.67, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 5.16 (d, J = 5.8 Hz, 1H), 5.53 (d, J = 5.8 Hz, 1H), 7.31-7.44 (m, 8H), 7.66 (d, J = 7.8 Hz, 2H), 10.33 (bs, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 63.97, 75.72, 123.29, 126.49, 127.27, 128.77, 132.49, 137.26, 174.87; IR ($CHCl_3$)

3553, 3295, 3048, 2949, 1760, 1601, 1384, 1313 cm^{-1}; MS (FAB) m/z (%) 299(M+1, 46), 179(100).

(3*R*,4*S*)-1-(Morpholinecarbonyl)-3-hydroxy-4-phenyl-2-azetidinone (8f): 83%; white solid; mp 55-57°C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.05 (bs, 1H), 3.56-3.78 (m, 8H), 5.00 (d, J = 5.9 Hz, 1H), 5.38 (d, J = 5.9 Hz, 1H), 7.24-7.40 (m, 5H).

(3*R*,4*S*)-1-(N,N-Dimethylcarbamoyl)-3-hydroxy-4-phenyl-2-azetidinone (8g): 88%; white crystal; mp 123-125°C; $_1$H NMR (250 MHz, $CDCl_3$) δ3.06 (bs, 6H, 4.98 (d, J=5.9 Hz, 1H), 5.35 (d, J=5.9 Hz, 1H), 7.29-7.39 (m, 5H).

(3*R*,4*S*)-1-*tert*-Butoxycarbonyl-4-phenyl-3-(1,1,1-trichloroethoxycarbonyl)-2-azetidinone (9a): To a solution of 99 mg (0.38 mmol) of 1-*tert*-butylcarbonyl-3-hydroxy-4-phenyl- 2-azetidinone, 5 mg of DMAP and 263 mL (2 mmol) of triethylamine in 5 mL of dichloromethane, was added at 0°C 105 mL (0.8 mmol) of 1,1,1-trichloroethyl-chloroformate. The reaction mixture was stirred overnight at room temperature. The organic layer was washed several times with brine, dried over $MgSO_4$ and concentrated. The crude solid was purified by chromatography on silica gel to yield 65 mg (40%) of O-protected β-lactam: White solid; mp 122-124°C; $[\alpha]D^{20}$ +28° (c 0.5, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.39 (s, 9H), 4.43 (d, J = 11.7 Hz, 1H), 4.55 (d, J = 11.7 Hz, 1H), 5.28 (d, J = 5.5 Hz, 1H), 5.76 (d, J = 5.5 Hz, 1H), 7.30 (m, 5H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 27.81, 60.80, 77.03, 78.76, 84.40, 127.73, 128.58, 129.09, 131.55, 147.71, 152.17, 160.34; IR ($CHCl_3$) 3016, 2976, 1819, 1771, 1732, 1683, 1244 cm^{-1}. Anal. Calcd for $C_{17}H_{18}Cl_3NO_6$: C, 46.54; H, 4.14; N, 3.19. Found: C, 46.33; H, 4.34; N, 3.33.

(3*R*,4*S*)-3-Acetoxy-1-*tert*-butoxycarbonyl-4-phenyl-2-azetidinone (9b): To a solution of 82 mg (0.3 mmol) of 1-*tert*-butylcarbonyl-3-hydroxy-4-phenyl-2-azetidinone, 5 mg of DMAP and 210 mL (1.5 mmol) of triethylamine in 5 mL of dichloromethane, was added at 0°C 58 mL (0.7 mmol) of acetic anhydride. The reaction mixture was stirred overnight at room temperature. The organic layer was washed several times with brine, dried over $MgSO_4$ and concentrated. The crude solid was purified by chromatography on silica gel to yield 71 mg (75%) of O-acetyl β-lactam: White solid; mp 63-64°C; $[\alpha]D^{20}$ +32.1° (c 0.81, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 1.37 (s, 9H), 1.65 (s, 3H), 5.22 (d, J = 5.5 Hz, 1H), 5.83 (d, J = 5.5 Hz, 1H), 7.23-7.33 (m, 5H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 19.71, 27.81, 60.84, 75.94, 84.07, 127.43, 128.31, 128.67, 132.44, 147.25, 162.39, 168.83; IR ($CHCl_3$) 3026, 2984, 1815, 1752, 1731, 1497, 1371, 1286, 1224, 1152, 1024 cm^{-1}. Anal. Calcd for $C_{16}H_{19}NO_5$: C, 62.94; H, 6.27; N, 4.59. Found: C, 63.17; H, 6.14; N, 4.52.

Example 54

To a suspension of NaH (35 mg in 1.0 mL of DME), was added at -10°C, a solution of 133 mg (0.15 mmol) of 7,10-ditroc-10-deacetylbaccatin III and 100 mg (0.30 mmol) of **5d** in 1.5 mL of DME. The reaction was monitored by TLC and quenched at -8°C by addition of brine. The aqueous layer was extracted with dichloromethane. The combined organic layers were washed with brine, dried over Na_2CO_3 and concentrated. The crude oil was purified by chromatography on silica gel using AcOEt/hexanes (1/2) as the eluant to give 148 mg of the coupling product 2'-EE-7,10-ditroc-Taxotère as a white solid (81% yield; 90% conversion yield) and 12 mg of 7,10-ditroc-10-deacetylbaccatin III (10% recovery).

The EE protecting group was removed by stirring

at room temperature 90 mg of 2′-EE-7,10-ditroc-Taxotère in 3 mL of THF and 2 mL of 0.5N HCl for 1 hr. The reaction mixture was diluted with dichloromethane. The organic phase was washed with sat. $NaHCO_3$ sol., brine dried over $MgSO_4$ and concentrated. The crude oil was purified by chromatography on silica gel using AcOEt/hexanes (1/2) as the eluant to give 60 mg (71%) of 2′-OH-7,10-ditroc-Taxotère as a white solid: Mp 154-155°C; $[\alpha]D^{20}$ -38° (c 0.74, CHCl3); ^1H NMR (250 MHz, $CDCl_3$) δ 1.19 (s, 3H), 1.26 (s, 3H), 1.35 (s, 9H), 1.85 (s, 3H), 1.95 (s, 3H), 2.04 (m, 1H), 2.34 (m, 2H), 2.39 (s, 3H), 2.62 (m, 1H), 3.90 (d, J = 6.4 Hz, 1H), 4.17 (d, J = 8.4 Hz, 1H), 4.32 (d, J = 8.4 Hz, 1H), 4.60 (d, J = 11.9 Hz, 1H), 4.64 (m, 1H), 4.78 (s, 2H), 4.91 (d, J = 11.9 Hz, 1H) , 4.95 (m, 1H), 5.26 (bd, J = 8.7 Hz, 1H), 5.46 (bd, J = 9.2 Hz, 1H), 5.54 (dd, J = 10.4, 7.1 Hz, 1H), 5.69 (d, J = 6.8 Hz, 1H), 6.21 (bt, J = 8.7 Hz, 1H), 6.24 (s, 1H), 7.32-7.35 (m, 5H), 7.50 (t, J = 7.5 Hz, 2H), 7.62 (t, J = 7.3 Hz, 1H), 8.10 (d, J = 7.5 Hz, 2H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 10.69, 14.63, 20.91, 22.47, 26.25, 28.14, 33.20, 35.21, 43.07, 46.91, 56.14, 72.17, 73.50, 74.10, 76.48, 77.33, 77.51, 78.55, 79.08, 80.23, 80.67, 83.61, 94.11, 126.70, 128.06, 128.70, 128.88, 130.12, 131.91, 133.79, 138.20, 142.48, 153.12, 153.17, 155.36, 166.82, 170.33, 172.78, 200.70; IR ($CHCl_3$) 3572, 3444, 3034, 2979, 1759, 1737, 1724, 1490, 1450, 1376, 1106 cm^{-1}.

Example 55

To a solution of 90 mg (0.1 mmol) of 7,10-ditroc-10-deacetylbaccatin III and 47 mg (0.14 mmol) of **5d** in 5 mL of THF, was added at -30°C 110 mL (0.11 mmol, 1M in THF) of sodium hexamethyldisilazide. The reaction was monitored by TLC and quenched by addition of brine. The aqueous layer was extracted with dichloromethane. The combined organic layers were washed with brine, dried over

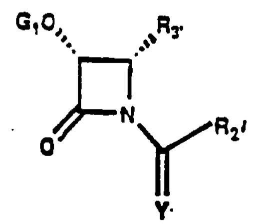
Na_2CO_3 and concentrated. The crude oil was purified by chromatography on silica gel using AcOEt/hexanes (1/2) as the eluant to give 117 mg of the coupling product 2'-EE-7,10-ditroc-TAXOTÈRE as a white solid (94%). All physical and spectral data are identical with those of 2'-EE-7,10-ditroc-TAXOTÈRE described in Example 54.

The Troc protecting group was removed by stirring at 60°C 50 mg of 7,10-ditroc-TAXOTÈRE in 1 mL of MeOH and 1 mL of AcOH in presence of 150 mg of zinc for 1 hr. The reaction mixture was filtrated and diluted with dichloromethane. The organic phase was washed with sat. $NaHCO_3$ sol., brine dried over $MgSO_4$ and concentrated. The crude oil was purified by chromatography on silica gel using AcOEt/hexanes (1/1) as the eluant to give 28 mg (80%) of TAXOTÈRE as a white solid: $[\alpha]_D^{20}$ -34° (c 0.7, EtOH); NMR (250 MHz, $CDCl_3$) δ 1.13 (s, 3H), 1.26 (s, 3H), 1.35 (s, 9H), 1.80 (s, 3H), 1.85 (m,), 1.90 (s, 3H), 2.24 (m, 2H), 2.39 (s, 3H), 2.55 (m,), 2.62 (m,), 3.53 (s,), 3.92 (d, J = 7.0 Hz,), 4.18 (d, J = 8.4 Hz,), 4.22 (m,), 4.32 (d, J = 8.4 Hz,), 4.66 (d, J = 6.9 Hz,), 6.19 (bt, J = 8.1 Hz,), 7.32-7.35 (m, 5H), 7.50 (t, J = 7.5 Hz, 2H), 7.62 (t, J = 7.3 Hz,), 8.10 (d, J = 7.5 Hz, 2H). These data are consistent with those reported for TAXOTÈRE by Mangatal, L. et al. (Ref. Mangatal, L.; Adeline, M.T.; Guénard, D.; Guéritte-Voegelein, F.; Potier, P. *Tetrahedron* **1989**, *45*, 4177.)

Although the invention has been described in conjunction with specific embodiments, it is evident that many alternatives and variations will be apparent to those skilled in the art in light of the foregoing description. Accordingly, the invention is intended to embrace all of the alternatives and variations that fall within the spirit and scope of the appended claims. The above references are hereby incorporated by reference.

We Claim:

1. A β-lactam of the formula:



in which

$R_{2'}$ represents an RO-, RS- or RR'N- in which R represents an unsubstituted or substituted straight chain or branched alkyl, alkenyl or alkynyl, cycloalkyl, heterocycloalkyl, cycloalkenyl, heterocycloalkenyl, carbocyclic aryl or heteroaryl; is a hydrogen or R as defined above; R and R′ can be connected to form a cyclic structure;

$R_{3'}$ represents an unsubstituted or substituted straight or branched alkyl, alkenyl or alkynyl radical, an unsubstituted or substituted cycloalkyl, cycloalkenyl radical, an unsubstituted or substituted carbocyclic aryl;

G_1 represents a hydrogen or a hydroxyl protecting group;

Y is oxygen or sulfur.

2. A β-lactam according to claim 1 in which

$R_{2'}$ represents a radical RO-, RS- or RR′N- in which R represents a straight chain or branched alkyl radical containing 1 to 10 carbon atoms, a straight chain or branched alkenyl radical containing 2 to 10 carbon atoms, or a straight chain or branched alkynyl radical containing 2 to 10 carbon atoms, a cycloalkyl radical containing 3 to 10 carbon atoms, a heterocycloalkyl radical containing 3 to 10 carbon atoms, a cycloalkenyl radical containing 3 to 10 carbon atoms, a heterocycloalkenyl radical containing 3 to 10 carbon

atoms, a polycycloalkyl radical containing 6 to 20 carbon atoms, an aryl radical containing 6 to 20 carbons, a heteroaryl radical containing 3 to 15 carbon atoms; these radicals being optionally substituted with one or more halogen, hydroxyl, alkoxy, aryloxy, heteroaryloxy, amino, alkylamino, dialkylamino, mercapto, alkylthio, arylthio, heteroarylthio, cyano, carboxyl, alkoxycarbonyl radicals, the alkyl portion of which contain 1 to 15 carbon atoms, aryloxycarbonyl the aryl portion of which containing 6 to 20 carbon atoms, or heteroaryloxycarbonyl the heteroaryl portion of which containing 3 to 15 carbon atoms; R′ is a hydrogen or R as defined above; R and R′ can be connected to form a cyclic structure which contains 2-10 carbon atoms;

$R_{3'}$ represents a straight chain or branched alkyl radical containing 1 to 10 carbon atoms, a straight chain or branched alkenyl radical containing 2 to 10 carbon atoms, or a straight chain or branched alkynyl radical containing 2 to 10 carbon atoms, a cycloalkyl radical containing 3 to 10 carbon atoms, a cycloalkenyl radical containing 3 to 10 carbon atoms, a polycycloalkyl radical containing 6 to 20 carbon atoms, or an aryl radical containing 6 to 20 carbons; these radicals being optionally substituted with one or more halogen, hydroxyl, alkoxy, aryloxy, heteroaryloxy, amino, alkylamino, dialkylamino, mercapto, alkylthio, arylthio, heteroarylthio, cyano, carboxyl, alkoxycarbonyl radicals, the alkyl portion of which contain 1 to 15 carbon atoms, aryloxycarbonyl the aryl portion of which contain 6 to 20 carbon atoms, or heteroaryloxycarbonyl the heteroaryl portion of which containing 3 to 15 carbon atoms.

3. A β-lactam according to claim 1 in which $R_{2'}$ represents an RO-, RS-, or RR′N- in which R is an unsubstituted or substituted alkyl radical selected from methyl, ethyl, propyl, isopropyl, butyl, isobutyl,

tert-butyl, pentyl, isopentyl, neopentyl, hexyl, isohexyl, heptyl, isoheptyl, octyl, isooctyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, 9-fluorenylmethyl, benzyl and adamantyl, or an alkenyl radical selected from vinyl and allyl, or an aryl radical selected from phenyl and naphthyl, or a heteroaryl radical selected from furyl, pyrrolyl, and pyridyl, or a cycloalkenyl radical selected from cyclopentenyl, cyclohexenyl and cycloheptenyl, or a heterocycloalkyl radical selected from an oxiranyl, tetrahydrofuryl, pyrrolidinyl, piperdinyl, tetrahydropyranyl, or a heterocycloalkenyl radical selected from dihydrofuryl, dihydropyrrolyl, dihydropyranyl, dihydropyridyl; R′ is a hydrogen or R as defined above; cyclic RR′N- radical includes aziridino, azetidino, pyrrolidino, piperidino or morpholino group;

$R_{3'}$ is an unsubstituted or substituted alkyl radical selected from methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, isopentyl, neopentyl, hexyl, isohexyl, heptyl, isoheptyl, octyl, isooctyl, cyclohexylmethyl, cyclohexylethyl, benzyl, phenylethyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, 9-fluorenylmethyl, benzyl and adamantyl, or an alkenyl radical selected from vinyl, allyl, 2-phenylethenyl, or an alkynyl radical selected from ethynyl and propargyl or an aryl radical selected from phenyl and naphthyl, or a cycloalkenyl radical selected from cyclopentenyl, cyclohexenyl and cycloheptenyl;

G_1 represents a hydrogen or a group protecting the hydroxyl function selected from methoxylmethyl (MOM), methoxyethyl (MEM), 1-ethoxyethyl (EE), benzyloxymethyl, (β-trimethylsilylethoxyl), methyl, tetrahydropyranyl, 2,2,2-trichloroethoxylcarbonyl (Troc), benzyloxycarbonyl (CBZ), tertbutoxycarbonyl (t-BOC), 9-fluorenylmethoxycarbonyl (Fmoc), 2,2,2-

trichloroethoxymethyl, trimethylsilyl, triethylsilyl, tripropylsilyl, dimethylethylsilyl, dimethyl(t-butyl)silyl, diethylmethylsilyl, dimethylphenylsilyl, diphenylmethylsilyl, acetyl, chloroacetyl, dichloroacetyl, trichloroacetyl and trifluoroacetyl.

4. A β-lactam according to claim 1 in which Y is oxygen and $R_{2'}$ represents RO- in which R is a methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, neopentyl, cyclohexyl, phenyl, benzyl, or 9-fluorenylmethyl; $R_{3'}$ is a phenyl, tolyl, 4-methoxyphenyl, 3,4-dimethoxyphenyl, 4-fluorophenyl, 4-trifluoromethylphenyl, 1-naphthyl, 2-phenylethenyl;

G_1 is a hydrogen, 1-ethoxyethyl (EE), 2,2,2-trichloroethoxylcarbonyl (Troc), trimethylsilyl, triethylsilyl or acetyl.

5. A β-lactam according to claim 1 in which Y is oxygen and $R_{2'}$ is a methylamino, ethylamino, propylamino, isopropylamino, butylamino, isobutylamino, tert-butylamino, neopentylamino, cyclohexylamino, phenylamino or benzylamino, dimethylamino, diethylamino, dipropylamino, dibutylamino, dipentylamino, dihexylamino, dicyclohexylamino, methyl(tert-butyl)amino, cyclohexyl(methyl)amino, methyl(phenyl)amino, pyrrolidino, piperidino or morpholino group;

G_1 is a hydrogen, 1-ethoxyethyl (EE), 2,2,2-trichloroethoxycarbonyl (Troc), trimethylsilyl, triethylsilyl or acetyl.

6. A β-lactam according to claim 1 in which Y is sulfur and $R_{2'}$ represents RO- in which R is a methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, neopentyl, cyclohexyl, phenyl, benzyl or 9-

fluorenylmethyl; $R_{3'}$ is a phenyl, tolyl, 4-methoxyphenyl, 3,4-dimethoxyphenyl, 4-fluorophenyl, 4-trifluoromethylphenyl, 1-naphthyl, 2-naphthyl;

G_1 is a hydrogen, 1-ethoxyethyl (EE), 2,2,2-trichloroethoxylcarbonyl (Troc), trimethylsilyl, triethylsilyl or acetyl.

7. A β-lactam according to claim 1 in which

Y is sulfur and R_2 is a methylamino, ethylamino, propylamino, isopropylamino, butylamino, isobutylamino, tert-butylamino, neopentylamino, cyclohexylamino, phenylamino, or benzylamino, dimethylamino, diethylamino, dipropylamino, dibutylamino, dipentylamino, dihexylamino, dicyclohexylamino, methyl(tert-butyl)amino, cyclohexyl(methyl)amino, methyl(phenyl)amino, pyrrolidino, piperidino, or morpholino group;

G_1 is a hydrogen, 1-ethoxyethyl (EE), 2,2,2-trichloroethoxylcarbonyl (Troc), trimethylsilyl, triethylsilyl or acetyl.

8. A β-lactam according to claim 1 in which

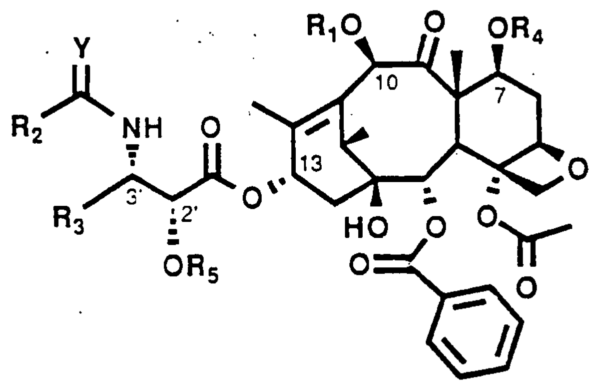
Y is oxygen, $R_{2'}$ represents RO- in which R is a methyl, ethyl, butyl, tert-butyl, phenyl or benzyl and R_2 is a phenyl, 2-phenylethenyl, cyclohexylmethyl or isobutyl;

Y is oxygen, $R_{2'}$ is an ethylamino, tert-butylamino, phenylamino, benzylamino, dimethylamino or morpholino group, and $R_{3'}$ is a phenyl;

Y is sulfur, $R_{2'}$ is a phenylamino, dimethylamino or morpholino group, $R_{3'}$ is a phenyl;

G_1 is a hydrogen or 1-ethoxyethyl (EE), 2,2,2-trichloroethoxylcarbonyl (Troc) or acetyl.

9. A process for the preparation of a taxane derivative of the formula



in which

R_1 represents a hydrogen or an acyl or an alkyl or an alkenyl or an alkynyl or an aryl or a heteroaryl radical or a hydroxyl protecting group;

R_2 represents an RO-, RS- or RR'N- in which R represents an unsubstituted or substituted straight chain or branched alkyl, alkenyl or aklynyl, cycloalkyl, heterocycloalkyl, cycloalkenyl, heterocycloalkenyl, aryl or heteroaryl; R' is a hydrogen or R defined above; R and R' can be connected to form a cyclic structure;

Y is oxygen or sulfur;

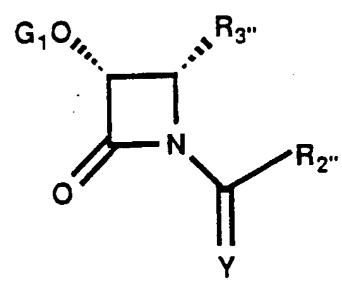
R_3 represents an unsubstituted or substituted straight chain or branched alkyl, alkenyl or alkynyl radical, an unsubstituted or substituted cycloalkyl, cycloalkenyl or an unsubstituted or substituted carbocyclic aryl;

R_4 represents a hydrogen or an acyl radical or an unsubstituted or substituted straight chain or branched alkyl, alkenyl or alkynyl radical, an unsubstituted or substituted cycloalkyl, heterocycloalkyl, cycloalkenyl or heterocycloalkenyl radical, an unsubstituted or substituted aryl or heteroaryl radical, or a hydroxyl group protecting group;

R_5 represents a hydrogen or a acyl radical or an unsubstituted or substituted straight chain or branched alkyl, alkenyl, or alkynyl radical, an unsubstituted or substituted cycloalkyl, heterocycloalkyl, cycloalkenyl or heterocycloalkenyl radical, an unsubstituted or substituted aryl or heteroaryl radical, or a hydroxyl

protecting group;

which comprises reacting a β-lactam of the formula



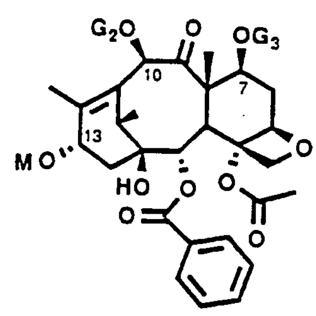
in which

Y is defined above; G_1 represents an hydroxyl protecting group;

$R_{2''}$ represents a radical R_2 defined above or a protected R_2 whenever R_2 includes one or more active hydrogens,

$R_{3''}$ represents a radical R_3 defined above or a protected R_3 whenever R_3 includes one or more active hydrogens;

with a baccatin III derivative of the formula:



in which M is an alkali metal or alkaline earth metal atom (ion);

G_2 represents a hydroxyl protecting group or an acyl radical or an unsubstituted or substituted straight chain or branched alkyl, alkenyl or alkynyl radical, an unsubstituted or substituted cycloalkyl, heterocycloalkyl, cycloalkenyl or heterocycloalkenyl radical, an

unsubstituted or substituted aryl or heteroaryl radical;

G_3 represents a hydroxyl group protecting group or an acyl radical or an unsubstituted or substituted straight chain or branched radical alkyl, alkenyl or alkynyl radical, an unsubstituted or substituted cycloalkyl, heterocycloalkyl, cycloalkenyl, heterocycloalkenyl radical, an unsubstituted or substituted aryl or heteroaryl.

10. The process according to claim 9, in which

R_2 represents a radical RO-, RS-, or RR'N- in which R represents a straight chain or branched alkyl radical containing 1 to 10 carbon atoms, a straight chain or branched alkenyl radical containing 2 to 10 carbon atoms, or a straight chain or branched alkynyl radical containing 2 to 10 carbon atoms, a cycloalkyl radical containing 3 to 10 carbon atoms, a heterocycloalkyl radical containing 3 to 10 carbon atoms, a cycloalkenyl radical containing 3 to 10 carbon atoms, a heterocycloalkenyl radical containing 3 to 10 carbon atoms, a polycycloalkyl radical containing 6 to 20 carbon atoms, an aryl radical containing 6 to 20 carbons, a heteroaryl radical containing 3 to 15 carbon atoms; these radicals being optionally substituted with one or more halogen, hydroxyl, alkoxy, aryloxy, heteroaryloxy, amino, alkylamino, dialkylamino, mercapto, alkylthio, arylthio, heteroarylthio, cyano, carboxyl, alkoxycarbonyl the alkyl portion of which contains 1 to 15 carbon atoms, aryloxycarbonyl the aryl portion of which containing 6 to 20 carbon atoms, or heteroaryloxycarbonyl the heteroaryl portion of which containing 3 to 15 carbon atoms; R' is a hydrogen or R defined above; R and R' can form a cyclic structure which contains 2-10 carbon atoms;

R_3 represents a straight chain or branched alkyl radical containing 1 to 10 carbon atoms, a straight chain or branched alkenyl radical containing 2 to 10 carbon

atoms, or a straight chain or branched alkynyl radical containing 2 to 10 carbon atoms, a cycloalkyl radical containing 3 to 10 carbon atoms, a cycloalkenyl radical containing 3 to 10 carbon atoms, a polycycloalkyl radical containing 6 to 20 carbon atoms, an aryl radical containing 6 to 20 carbons; these radicals being optionally substituted with one or more halogen, hydroxyl, alkoxy, aryloxy, heteroaryloxy, amino, alkylamino, dialkylamino, mercapto, alkylthio, arylthio, heteroarylthio, cyano, carboxyl, alkoxycarbonyl, the alkyl portion of which containing 1 to 15 carbon atoms, aryloxycarbonyl, the aryl portion of which contains 6 to 20 carbon atoms, or heteroaryloxycarbonyl the heteroaryl portion of which containing 3 to 15 carbon atoms;

$R_{2'}$ represents a radical R_2 defined above or a protected R_2 whenever R_2 includes one or more active hydrogens;

$R_{3'}$ represents a radical R_3 defined above or a protected R_3 whenever R_3 includes one or more active hydrogens.

11. The process according to claim 9, wherein

R_2 represents an RO-, RS-, or RR'N- in which R is an unsubstituted or substituted alkyl radical selected from methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, isopentyl, neopentyl, hexyl, isohexyl, heptyl, isoheptyl, octyl, isooctyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, and adamantyl, or an alkenyl radical selected from vinyl and allyl, or an aryl radical selected from phenyl and naphthyl, or a heteroaryl radical selected from furyl, pyrrolyl, and pyridyl, or a cycloalkenyl radical selected from cyclopentenyl, cyclyhexenyl and cycloheptenyl, or a heterocycloalkyl radical selected from an oxiranyl, tetrahydrofuryl, pyrrolidinyl, piperidinyl,

tetrahydropyranyl, or a heterocycloalkenyl radical selected from dihydrofuryl, dihydropyrrolyl, dihydropyranyl, dihydropyridyl; R′ is a hydrogen or R defined above; cyclic RR′N- radical includes aziridino, azetidino, pyrrolidino, piperidino or morpholino group;

R_3 is an unsubstituted or substituted alkyl radical selected from methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, isopentyl, neopentyl, hexyl, isohexyl, heptyl, isoheptyl, octyl, isooctyl, cyclohexylmethyl, cyclohexylethyl, benzyl, phenylethyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, and adamantyl, or an alkenyl radical selected from vinyl, allyl or an alkynyl radical selected from ethynyl and propargyl or an aryl radical selected from phenyl and naphthyl, or a cycloalkenyl radical selected from cyclopentenyl, cyclohexenyl and cycloheptenyl.

R_{2*} represents a radical R_2 defined above or a protected R_2 wherever R_2 includes one or more active hydrogens;

R_{3*} represents a radical R_3 defined above or a protected R_3 wherever R_3 includes one or more active hydrogens;

G_1 represents a group protecting the hydroxyl function selected from methoxylmethyl (MOM), methoxyethyl (MEM), 1-ethoxyethyl (EE), benzyloxymethyl, (β-trimethylsilyl-ethoxyl)-methyl, tetrahydropyranyl, 2,2,2-trichloroethoxylcarbonyl (Troc), benzyloxycarbonyl (CBZ), tert-butoxycarbonyl (t-BOC), 9-fluorenylmethoxycarbonyl (Fmoc), 2,2,2-trichloroethoxymethyl, trimethylsilyl, triethylsilyl, tripropylsilyl, dimethylethylsilyl, dimethyl(t-butyl)silyl, diethylmethylsilyl, dimethylphenylsilyl and diphenylmethylsilyl, acetyl, chloroacetyl, dichloroacetyl, trichloroacetyl and trifluoroacetyl;

G_2 represents an acetyl or a 2,2,2-trichloroethoxycarbonyl (Troc) group;

G_3 represents a 2,2,2-trichloroethoxycarbonyl (Troc) or silyl group selected from trimethylsilyl, triethylsilyl, tripropylsilyl, dimethylethylsilyl, dimethylphenylsilyl, dimethyl(t-butyl)silyl, diethylmethylsilyl and diphenylmethylsilyl.

12. The process according to claim 9, wherein M is an alkali metal.

13. The process according to claim 10, wherein M is an alkali metal selected from lithium, sodium and potassium.

14. The process according to claim 11, wherein M is sodium or potassium.

15. The process according to claim 11 wherein R_1 is a hydrogen, an acetyl or an trichloroethoxycarbonyl (Troc); R_4 is a hydrogen, a triethylsilyl or a trichloroethoxycarbonyl (Troc); R_5 is a hydrogen, a triethylsilyl or ethoxyethyl.

16. The process according to claim 11 wherein R_2 represents RO- in which R is a methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, neopentyl, cyclohexyl, phenyl, benzyl or 9-fluoroenylmethyl; R_3 is a phenyl, tolyl, 4-methoxyphenyl, 3,4-dimethoxyphenyl, 4-fluorophenyl, 4-trifluoromethylphenyl, 1-naphthyl, 2-naphthyl and 2-phenylethenyl; R_5 is a hydrogen.

17. The process according to claim 11 wherein R_2 is a methylamino, ethylamino, propylamino, isopropylamino, butylamino, isobutylamino, tert-

butylamino, neopentylamino, cyclohexylamino, phenylamino or benzylamino, dimethylamino or morpholino group; R_5 is a hydrogen.

18. The process according to claim 9 wherein R_1 is a hydrogen or a acetyl; R_2 (= R_2^*) is tert-butoxy or tert-butylamino; R_3 (= R_3^*) is a phenyl; Y is oxygen; R_4 is a hydrogen; R_5 is a hydrogen; G_1 is an ethoxyethyl, triethylsilyl or trichloroethoxycarbonyl (Troc); M is sodium or potassium.

INTERNATIONAL SEARCH REPORT

Inte   onal Application No
PCT/US 94/00669

A. CLASSIFICATION OF SUBJECT MATTER
IPC 5 C07D205/08 C07D305/14

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 5 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	TETRAHEDRON, (INCL. TETRAHEDRON REPORTS) vol. 48, no. 34 , 1992 , OXFORD GB pages 6985 - 7012 I. OJIMA ET AL. 'New and efficient approaches to the semisynthesis of taxol and its C-13 side chain analogs by means of beta-lactam synthon method' cited in the application see the whole document ---	1-18

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

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Date of the actual completion of the international search	Date of mailing of the international search report
14 April 1994	28.04.94

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Chouly, J

Form PCT/ISA/210 (second sheet) (July 1992)

Inte onal Application No
PCT/US 94/00669

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	JOURNAL OF ORGANIC CHEMISTRY vol. 56, no. 5 , 1991 , EASTON US pages 1681 - 1683 I. OJIMA ET AL. 'Efficient and practical asymmetric synthesis of the taxol C-13 side chain, N-benzoyl-(2R,3S)-3-phenylisoserine, and its analogues via chiral 3-hydroxy-4-aryl-beta-lactams through chiral ester enolate-imine cyclocondensation' cited in the application see the whole document	1-18
Y	EP,A,0 400 971 (FLORIDA STATE UNIVERSITY) 5 December 1990 cited in the application see claims	1-18
P,X	WO,A,93 06093 (FLORIDA STATE UNIVERSITY) 1 April 1993 see pages 15, 28-33 and claims	1-18
P,Y	EP,A,0 525 589 (BRISTOL-MYERS SQUIBB COMPANY) 3 February 1993 see the whole document	1-18

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 94/00669

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
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